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Review article

Clues of HLAs, metabolic SNPs, and epigenetic factors in T cell-mediated drug hypersensitivity reactions

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ABSTRACT

Drug hypersensitivities are common reactions due to immunologic responses. They are of utmost importance because they may generate severe and fatal outcomes. Some drugs may cause Adverse Drug Reactions (ADRs), such as drug hypersensitivity reactions (DHRs), which can occur due to the interaction of intact drugs or their metabolites with Human Leukocyte Antigens (HLAs) and T cell receptors (TCRs). This type develops over a period of 24–72 h after exposure and is classified as type IV of DHRs. Acute generalized exanthematic pustulosis (AGEP), Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) are types of Severe Cutaneous Adverse Reactions (SCARs). In this review, we aim to discuss the types of ADRs, the mechanisms involved in their development, and the role of immunogenetic factors, such as HLAs in type IV DHRs, single-nucleotide polymorphisms (SNPs), and some epigenetic modifications, e.g., DNA/histone methylation in a variety of genes and their promoters which may predispose subjects to DHRs. In conclusion, development of promising novel in vitro or *in vivo* diagnostic and prognostic markers is essential for identifying susceptible subjects or providing treatment protocols to work up patients with drug allergies as personalized medicine.

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Key points

T cell-mediated drug reactions are rare life-threatening conditions. Timely identification of susceptible subjects or management of patients with such drug allergies may be of utmost importance.

1. Background

1.1. Adverse drug reactions

Every drug carries the risk of causing a variety of side effects. These adverse drug reactions (ADRs), often due to medication errors, account for 3–6% of hospital admissions and occur in 10%–15 % of hospitalized patients. According to the World Health Organization (WHO), ADRs are unintended, harmful, and occasionally life-threatening effects of a medication. They typically arise from a drug's inherent biological activity, often through pharmacological interactions with immunogenetic factors, such as Human Leukocyte Antigens (HLAs), also known as the major histocompatibility complex (MHC), or due to drug metabolism, rather than from the drug itself [1,2]. HLAs are a number of surface molecules that present either foreign or self-peptide antigens to T cells. They are the most

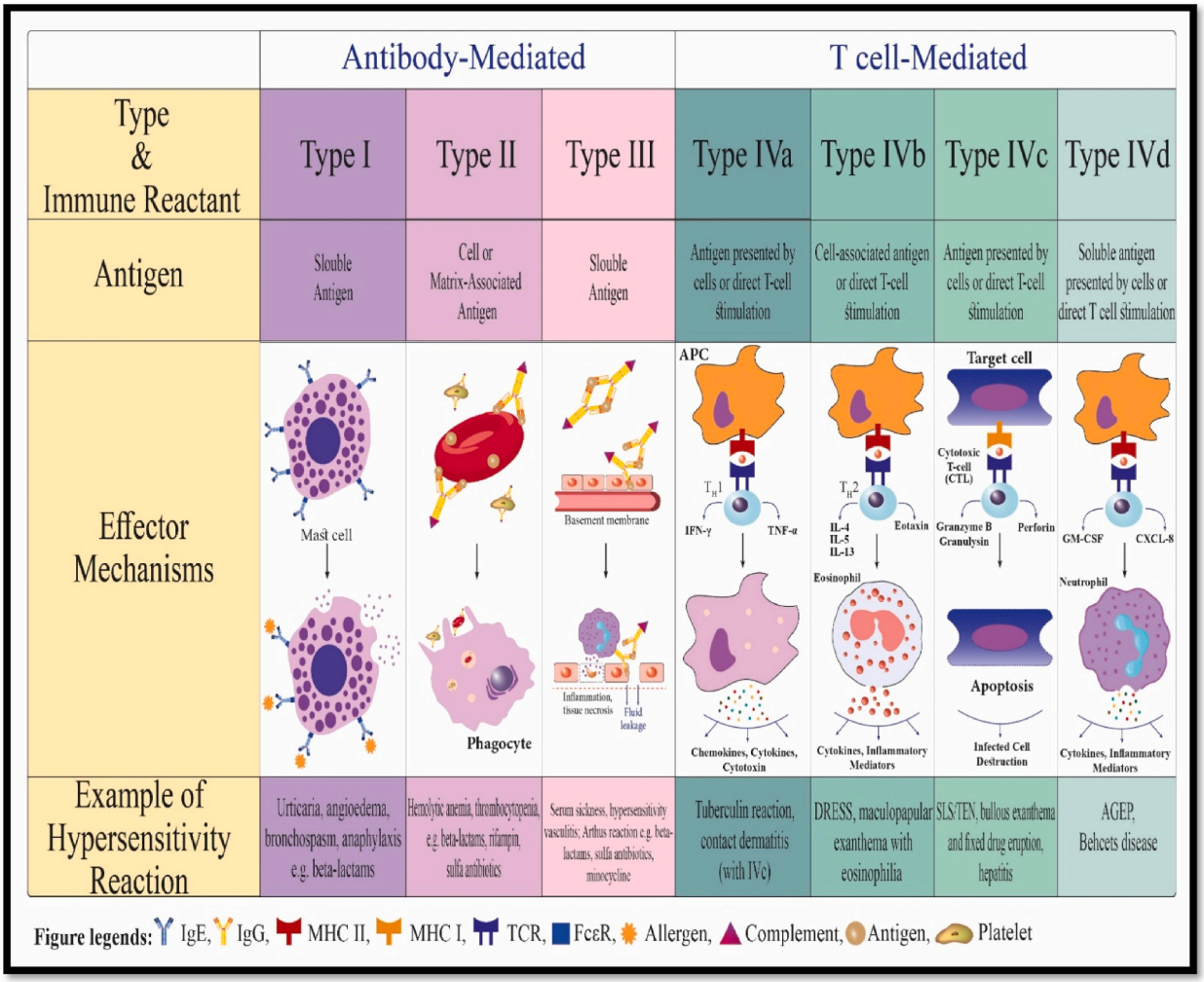

Fig. 1. Revised Gell and Coombs classification of drug reactions. Drugs may evoke all types of immune reactions. Although all reactions are fundamentally T-cell regulated, the effector cells depend mechanistically on antibody-mediated effector functions (type I–III) or T-cell/cytokine-dependent functions (type IVa–IVd). Type I reactions are called IgE-mediated. Cross-linking of IgE antibodies on high-affinity IgE receptors (Fc-IgE-RI) on mast cells and basophils lead to degranulation and release of inflammatory mediators. Type II reactions are IgG-mediated and generate cell destruction because of complement activation or interaction with Fc-receptor-bearing immune cells. Type III reactions are also IgG-mediated: complement deposition and activation in small vessels and recruitment of neutrophilic granulocytes via Fc-IgG receptor interaction. T cell-mediated reactions rely on T cell-antigen presenting cell (APC) interaction and cytokine and chemokine secretion. Adapted with permission from Ref. [7].

polymorphic loci in the human genome [3]. ADRs are categorized into Type A: pharmacologically-mediated and Type B: drug hypersensitivity reactions (DHRs). Type A reactions, approximately 80 % of the reactions, are referred to as predictable, dose-dependent, and prevalent reactions that occur due to the pharmacologic inherence of a drug. For example, bradycardia following propranolol consumption or hair growth following minoxidil consumption [4]. On the other hand, Type B reactions, nearly 20 % of the reactions, are unpredictable, rare, and dose-independent reactions, which are not owing to the pharmacologic nature of a drug [5]. In other words, these DHRs are either non-immune-mediated or immune-mediated allergic reactions ranging from IgE-mediated (type I), cytotoxic (type II), immune complex (type III), and cell-mediated (type IV) hypersensitivities, according to Gell-Coombs classification. Type B ADRs encompass drug intolerance, idiosyncratic reactions, and hypersensitivity reactions. Drug intolerance refers to the occurrence of adverse effects when a drug is administered at therapeutic or subtherapeutic doses. Idiosyncratic reactions are characterized by unusual responses that cannot be fully explained by the known pharmacologic mechanisms of the drugs. Hypersensitivity reactions, on the other hand, encompass both immunological and non-immunological reactions [2]. Clinical manifestations of type B reactions consist of mild presentations, such as a maculopapular rash or urticaria to severe reactions, such as anaphylaxis or Severe Cutaneous Adverse Reactions (SCARs) [6]. DHRs commonly occur due to immunologic reactions that are categorized into four groups. Drug-specific T lymphocytes play important roles in cell-mediated immunity. Four possible mechanisms may be hypothesized for drug presentation to T cells, clarifying the interaction of HLA and TCR in DHRs. The use of different drugs has become increasingly common, leading to a rise in the incidence of DHRs, resulting in serious consequences, including reduced therapeutic efficacy, unexpected side effects, and even life-threatening reactions. It is crucial to understand the mechanisms and clinical impact of these interactions to ensure the safe and effective use of drugs. To this end, prompt recognition and management of DHRs can help prevent or mitigate adverse outcomes, leading to improved patient safety and better treatment outcomes. Upon drug consumption, cellular and molecular patterns of immune cells at the site of inflammation will delineate the fate of immune responses. The interplay between $CD4^+$ and $CD8^+$ T cells and predisposing genes such as HLAs and metabolic single nucleotide polymorphisms (SNPs) and their expression via epigenetic variations specifies the type, severity, outcome, and underlying mechanisms of DHRs. Precision medicine strategies potentially facilitate prediction of reactions and earlier diagnosis of severity of DHRs. Identifying culprit drugs and avoiding cross-reactive agents will broaden drug choice for patients. In this review, we aim to discuss the types of ADRs, the mechanisms involved in the development of DHRs and drug-specific T cells, and the role of immunogenetic factors, such as HLAs, metabolic SNPs, and epigenetic factors in type IV DHRs. To this end, we retrieved publications about DHRs through ScienceDirect, PubMed, Scopus, Google Scholar, and Medline databases.

1.2. Categorization of DHRs based on etiology

Although DHRs are unpredictable events ranging from immediate to delayed type reactions, increasing knowledge about mechanisms of immunologic-pharmacologic interactions facilitated the classification of these reactions. In the following, we categorize heterogeneous DHRs into five main groups and describe their features (Fig. 1).

1.3. Non-allergic hypersensitivity reactions

These reactions, which comprise 12 % and 77 % of HDRs and all hypersensitivity reactions, respectively [8], are sometimes called ''pseudoallergic'' reactions because their clinical manifestations look like allergic urticaria or angioedema. Drugs such as the antimicrobial vancomycin (which may cause Red man syndrome) [9], nonsteroidal anti-inflammatory drugs (NSAIDs), neuromuscular blockers for anesthesia, opioid analgesics, such as morphine, radiocontrast media, and a variety of other less often used medications can directly stimulate degranulation of mast cells and release of histamine [10].

1.4. Type I drug hypersensitivity reactions

Types I, II, and III hypersensitivities are mediated by antibodies. Type I DHRs, which constitute 3 % of type B reactions [8], are commonly observed within 1–6 h after drug consumption and involve the IgE-mediated release of inflammatory mediators, such as histamine, cysteinyl Leukotrienes, heparin, tryptase, platelet-activating factor (PAF), and prostaglandins, which can lead to an inflammatory condition [9]. In this context, immediate reactions can be triggered via IgE-dependent (sometimes IgE-independent) routes of mast cell degranulation. Of note, they exhibit similar manifestations caused by the release of the above-mentioned mediators [11]. IgE binds to both its high-affinity receptor (FcεRI) on the surface of mast cells and basophils and its low-affinity IgE receptor (FcεRII or CD23) on several hematopoietic cells such as B cells) to amplify humoral and cellular immune responses [12].

Pharmaceutical compounds usually have a relatively low molecular weight and need to form complexes with host proteins to provoke an immune response. These complexes act as antigenic sites that can be detected by specific immunoglobulin E (IgE) antibodies or T cells, including $CD4^+$ T helper cells (Th) and $CD8^+$ cytotoxic T cells (TCTL). During the initial contact with the drug, it activates Th2 lymphocytes, which then prompt B lymphocytes to generate specific IgE antibodies. These antibodies attach to the FcεRI receptors on mast cells and basophils. When exposed to the drug again, cross-linking of at least two bound IgE molecules initiates degranulation and the release of mediators [11]. Type I allergic reactions can present with a variety of symptoms ranging from itching and swelling to hives, conjunctivitis, nasal inflammation, angioedema, bronchospasm, and gastrointestinal issues such as vomiting, abdominal pain, diarrhea, and nausea. In some cases, they can lead to anaphylaxis. A classic example of a type I reaction is an allergy to β-lactam antibiotics. Other drugs that can trigger these reactions include quinolones, anesthetic agents like chlorhexidine, and neuromuscular blocking agents like rocuronium [13,14].

1.5. Type II drug hypersensitivity reactions

Type II DHRs, also known as cytotoxic hypersensitivity and antibody-dependent cell-mediated cytotoxicity (ADCC), are severe and potentially life-threatening, occurring within minutes to hours. These reactions can impact various organs and tissues through several mechanisms. Although the target antigens are often endogenous, drugs can bind to cell membranes, leading to drug-induced immune hemolytic anemia, granulocytopenia, or thrombocytopenia. IgM or IgG antibodies attach to the target cells, and then non-phagocytic leukocytes with Fc receptors (such as natural killer cells, monocytes, neutrophils, and eosinophils) eliminate the coated cells through ADCC [15].

Drug-induced hemolytic anemias, which are identified by the presence of IgG antibodies and complement-mediated cytotoxicity or autoantibodies, can occur after the use of certain medications like penicillins, quinidine, α-methyldopa, and specific cephalosporins. With penicillin-induced reactions, it's believed that an atypical anti-penicillin antibody, likely due to specific binding to surface proteins, plays a role. Drug-induced thrombocytopenia, a condition where platelet counts drop, has been reported with medications such as quinine, quinidine, propylthiouracil, gold salts, acetaminophen, vancomycin, and sulfonamides. This decrease in platelet count is thought to happen because immune complexes attach to platelet membranes. Cytotoxic antibodies from drugs like pyrazolones, thiouracil, sulfonamides, anticonvulsants, and phenothiazines can lead to the destruction of peripheral neutrophils, resulting in granulocytopenia [10].

1.6. Type III drug hypersensitivity reactions

Type III hypersensitivity, or immune complex-mediated hypersensitivity, is triggered by soluble immune complexes formed when antigens bind to antibodies, usually of the IgG class and sometimes IgM. When these immune complexes deposit in tissues, they can activate the complement system, leading to potential mast cell degranulation, leukocyte recruitment, and inflammation caused by anaphylatoxins. These reactions typically develop 3–10 h after exposure to the antigen. The antigens involved can be endogenous, as in the DNA/anti-DNA/complement deposits in the kidneys of patients with systemic lupus erythematosus (SLE). Exogenous antigens like anti-lymphocyte globulins, Hymenoptera venoms, streptokinase, and certain vaccines can lead to classic serum sickness reactions. When antibodies bind to some drugs, they can create immune complexes that harm glomeruli and vascular walls [9]. For instance, erythema nodosum leprosum happens in a leprosy patient's skin under dapsone treatment [16]. The Jarisch-Herxheimer reaction can occur in people with syphilis who are being treated with penicillin. This reaction is a rapid inflammatory response to the release of bacterial toxins following the death of the pathogens. In addition, certain medications can cause serum sickness-like reactions. These drugs include penicillins, cephalosporins, ciprofloxacin, tetracycline, sulfonamides, lincomycin, carbamazepine, non-steroidal anti--inflammatory drugs (NSAIDs), allopurinol, phenytoin, griseofulvin, thiouracil, propranolol, captopril, barbiturates, gold salts, and monoclonal antibodies [10].

1.7. Type IV drug hypersensitivity reactions

Unlike types I, II, III hypersensitivity reactions, delayed-type or cell-mediated hypersensitivities, classified as type IV, are mediated by antigen-specific T cells. They include 5 % of DHRs and develop over a period of 24–72 h [17]. Even though DHRs constitute only a small portion of all unwanted events, they are highly important because they cause severe and fatal reactions. Acute generalized exanthematic pustulosis (AGEP), Stevens-Johnson syndrome (SJS)/Lyell syndrome/toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) cause SCARs with a high mortality rate of 5 %, 34 %, and 2–10 %, respectively [9].

Type Iva reactions: In cases of allergic contact dermatitis, the key immune cells that release interferon-γ and initiate a proinflammatory response are Th1 cells and macrophages. These cells promote the secretion of tumor necrosis factor-alpha (TNF-α) and interleukin-12 (IL-12), driving the inflammatory process.

Type IVb reactions: Th2 cells, which generate specific cytokines like IL-4, IL-13, and IL-5, encourage B cell proliferation, leading to plasma cell activation and the production of IgE and IgG4. Along with eosinophils, these cells are central to the immune response. This pattern can explain why certain drug-induced skin rashes contain a high number of eosinophils, providing insights into the mechanisms behind DRESS [18].

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a medical condition that presents with a diverse skin rash, changes in blood composition such as increased eosinophils and atypical lymphocytes, swelling of lymph nodes, and involvement of internal organs. DRESS is associated with significant non-specific activation of T-cells and the release of inflammatory substances [19]. In DRESS/DIHS, there is an accumulation of Th1/Th2 $CD4^+$ and $CD8^+$ T cells, plasma dendritic cells (DCs), and monocytes in the dermis (skin layer). The dendritic cells produce the chemokine CCL17, which recruits CCR4-positive Th2 helper T cells to the site. These TH2 cells, along with group 2 innate lymphoid cells (ILC2s), then produce IL-5 to activate and promote the migration of eosinophils. The eosinophils then drive the inflammatory response. Additionally, there is an observed presence of cytokines like TNF-α, IFN-γ (from Th1 cells), IL-4, IL-5, and IL-13 (from Th2 cells) along with the reactivation of human herpesvirus (HHV) and the involvement of regulatory T (Treg) cells in the skin lesions [20]. Sequential herpesvirus reactivation has been noted, with a delay in onset that can last up to 8 weeks and a drawn-out course with frequent relapses. This condition has also been associated with several terms, such as anticonvulsant hypersensitivity syndrome, allopurinol hypersensitivity syndrome, and drug-induced pseudolymphoma.

In cases of DRESS, drug causality is highly likely in about 80 % of cases. A European study revealed that anticonvulsants, allopurinol, sulfonamides, and antibiotics were responsible for 96 % of DRESS cases. Additionally, anti-retroviral medications, particularly

nevirapine and abacavir, are commonly linked to this syndrome. However, it is crucial to recognize that hypersensitivity reactions to abacavir often have an earlier onset and present with different symptoms than typical DRESS. Therefore, severe adverse reactions to abacavir are more accurately described as abacavir hypersensitivity. Moreover, the prevalent African allele HLA-B*53:01 appears to play a role in the development of DRESS syndrome in individuals taking the HIV medication raltegravir. While the exact mechanisms behind this immune-mediated process are not yet fully understood, computer simulations indicate that raltegravir may be able to bind within the antigen-binding region of the HLA-B*53:01 molecule, but not within the similar HLA-B*35:01 molecule [21]. Additionally, the HLA-C*04:01 allele has been associated with nevirapine-induced DRESS syndrome in individuals from Malawi [22].

1.8. Type IVc reactions

T cells are key players in the immune response, and their capacity to directly destroy target cells is mediated by substances like granzyme B, granulysin, and FAS ligand. This mode of action is often seen in skin rashes like maculopapular exanthemas, but it is more prevalent in severe cutaneous drug reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis.

Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN): is a drug-specific $CD8^+$ T cell-mediated cytotoxic response [19]. In SJS and TEN, multiple mucous membranes are typically affected, often leading to significant conjunctival damage. Internal organs may also be involved, and a notable reduction in lymphocytes, particularly $CD4^+$ T cells, has been observed. SJS and TEN are severe manifestations of the same condition, distinguished primarily by the percentage of body surface area (BSA) with skin detachment: SJS involves less than 10 % of the BSA, while TEN affects more than 30 %. Cases with 10–30 % detached BSA are considered overlap forms of SJS/TEN. The main characteristic of SJS/TEN is full-thickness necrosis of the epidermis. Although immune cell infiltration is typically minimal in skin biopsies, blister fluid analysis reveals a high concentration of lymphocytes and monocytes in later stages of the condition. The most common triggers for SJS/TEN are aromatic anticonvulsants, allopurinol, sulfonamides, NSAIDs, and antibiotics. Nonetheless, other factors may be responsible for about 15 % of cases. In children, idiopathic cases of SJS/TEN are more prevalent, and a small subset of these cases may be linked to infectious agents such as Mycoplasma pneumoniae. Furthermore, a variant of Coxsackie virus A6 has been identified as a cause of a severe blistering condition that resembles SJS/TEN, particularly in pediatric cases. Mortality rates for SJS/TEN correlate with the extent of body surface area (BSA) affected. Moreover, individuals who survive SJS/TEN face a higher risk of several complications, such as skin scarring, dyspigmentation, dental issues, genitourinary problems, pulmonary complications, and ocular lesions. These effects can significantly reduce a patient's quality of life and contribute to the chronic nature of SJS/TEN.

1.9. Type IVd reactions

Acute generalized exanthematic pustulosis (AGEP) is a medical condition characterized by the rapid appearance of numerous sterile pustules on a reddened skin background, often accompanied by fever and elevated neutrophil counts. It is a rare adverse drug reaction (ADR), with an estimated incidence ranging from one to five cases per million people annually [23]. The immune responses in acute generalized exanthematous pustulosis (AGEP) are driven by CXCL8 (interleukin 8) and granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-4, IL-5, IL-13, IFN-γ, TNF-α, IL-17, and IL-22 secreted from Th17 $CD4^+$ T cells. The cytokine IL-8 plays a key role in recruiting neutrophils and T cells to the epidermis, leading to the formation of sterile pustules [20]. These T cells attract neutrophilic granulocytes and inhibit their apoptosis, significantly contributing to the development of AGEP. Although AGEP is typically associated with drug reactions, especially to aminopenicillins, other factors can lead to skin rashes, including coexisting viral infections, particularly those caused by herpes viruses like Epstein-Barr Virus (EBV), Cytomegalovirus (CMV), and Human Herpesvirus 6 (HHV-6), parvovirus B19, coxsackie B4, Mycoplasma pneumoniae, mercury exposure and spider bites as well as HIV [24].

Drug-induced liver injury (DILI): Drug-induced liver injury (DILI), also referred to as drug-induced hepatitis, is a condition where the liver is harmed by the toxic effects or allergic reactions caused by certain drugs. It can affect both healthy people and those with pre-existing severe liver conditions. T cells, especially $CD8^+$ T cells, play a crucial role in causing liver injury by responding to drug-altered hepatic proteins presented by antigen-presenting cells (APCs). These interactions can result in hepatocyte damage, thus intensifying the severity of DILI. T cells are instrumental in identifying drug-related antigens and can induce liver damage through several mechanisms: APCs present hepatic proteins modified by drugs or metabolites, which activate T cells. The article points out the specific role of MHC class I molecules in presenting these antigens to $CD8^+$ T cells, triggering cytotoxic responses that characterize DILI. Once activated, T cells secrete cytokines that aggravate liver inflammation and damage. For instance, $CD8^+$ T cells can emit granzymes and other cytotoxic substances that directly cause hepatocyte death [25]. The progression from acute to chronic DILI may involve sustained T cell responses, particularly if the immune reaction to the drug continues even after it is discontinued. In addition, genetic factors, such as certain HLA alleles, modulate the immune response by T cells in DILI and are closely linked with increased susceptibility to DILI, underscoring the critical interaction between drug metabolites and T cells facilitated by these molecules in genetically predisposed individuals. $CD4^+$ T cells can execute their effector functions via membrane molecules that either deliver co-stimulatory signals, such as CD40L and OX40L, or trigger apoptosis through membrane interactions. The identification of HLA alleles as risk factors for DILI, such as flucloxacillin (B57:01), ximelagatran (DRB1*07:01), and lumiracoxib (DRB1*15:01), supports the theory of an immune mechanism. However, there is a lack of biological evidence demonstrating HLA restriction of drug-responsive cytotoxic T cells [26]. Clones responsive to flucloxacillin were also isolated from a patient positive for HLA-B*44:02/55:01, but these clones were exclusively $CD4^+$. Together, these findings suggest that immune responses play a role in the development of liver injury induced by Flucloxacillin [27].

While the exact immunopathogenesis of DILI is still unclear, its mechanisms may involve direct toxic effects, metabolic

disturbances, and both metabolic and allergic idiosyncrasies. Idiosyncrasies may be related to genetic polymorphisms found in cytochrome P450 enzymes (CYP450) and certain HLAs [28]. Symptoms of drug-induced liver injury (DILI) can include fatigue, nausea, abdominal pain, itching or jaundice (pruritus/icterus), coagulopathy, and elevated levels of enzymes such as aspartate aminotransferase (ASAT), alkaline phosphatase (AP), and bilirubin due to drugs like flucloxacillin and amoxicillin. The mortality rate for DILI can reach up to 10 %. In DILI, various drug-specific signaling pathways may influence interactions between hepatocytes and immune cells. When hepatocytes are exposed to toxic drugs like sulfamethoxazole or flucloxacillin, they can trigger dendritic cells to release proinflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 alpha and beta (IL-1α, IL-1β). Conversely, exposure to non-toxic drugs leads to a different secretion pattern, with interferon-gamma (IFN-γ), interleukin-10 (IL-10), interleukin-12 (IL-12), and interleukin-17A [11].

Drug-induced renal injury (DIRI): Drug-induced renal injury (DIRI) can cause predictable, cumulative dose-dependent toxicity or idiosyncratic, dose-independent toxicity during or after drug administration, as seen with penicillamine and contrast mediums. It can manifest clinically as acute renal failure, chronic renal failure, nephrotic syndrome, or tubulopathy. While cumulative dose-dependent renal toxicity can often be predicted and prevented, idiosyncratic renal toxicity is less predictable and may not be preventable. A more comprehensive understanding of DIRI can guide appropriate responses to mitigate the risk of renal toxicity. To minimize DIRI, it is crucial to identify high-risk individuals and weigh the nephrotoxic risk against the expected benefits of administering the drug. This approach can help reduce the incidence of DIRI and support safer medication practices [29].

1.10. Mechanisms proposed for the development of drug-specific T cells

In patients with non-immediate DHRs, drug-specific T cells are the main cells that become stimulated. This can occur through the covalent binding of drug molecules to carrier proteins that are then presented to T cells by APCs such as B cells. However, the culprit drug can also directly and non-covalently bind to immune receptors, leading to T cell activation different mechanisms. The specific mechanisms involved can lead to the activation of different subsets of drug-specific T cells, such as $CD4^+$ helper T cells (Th1, Th2, and Th17 subtypes) and $CD8^+$ cytotoxic T cells. These activated T cells can then contribute to the pathogenesis of DHRs through various effector functions, including mediating cytotoxicity, releasing inflammatory cytokines, and helping coordinate broader immune responses involving other cell types like B cells, mast cells, and eosinophils. By elucidating activation mechanisms of drug-specific T cells,

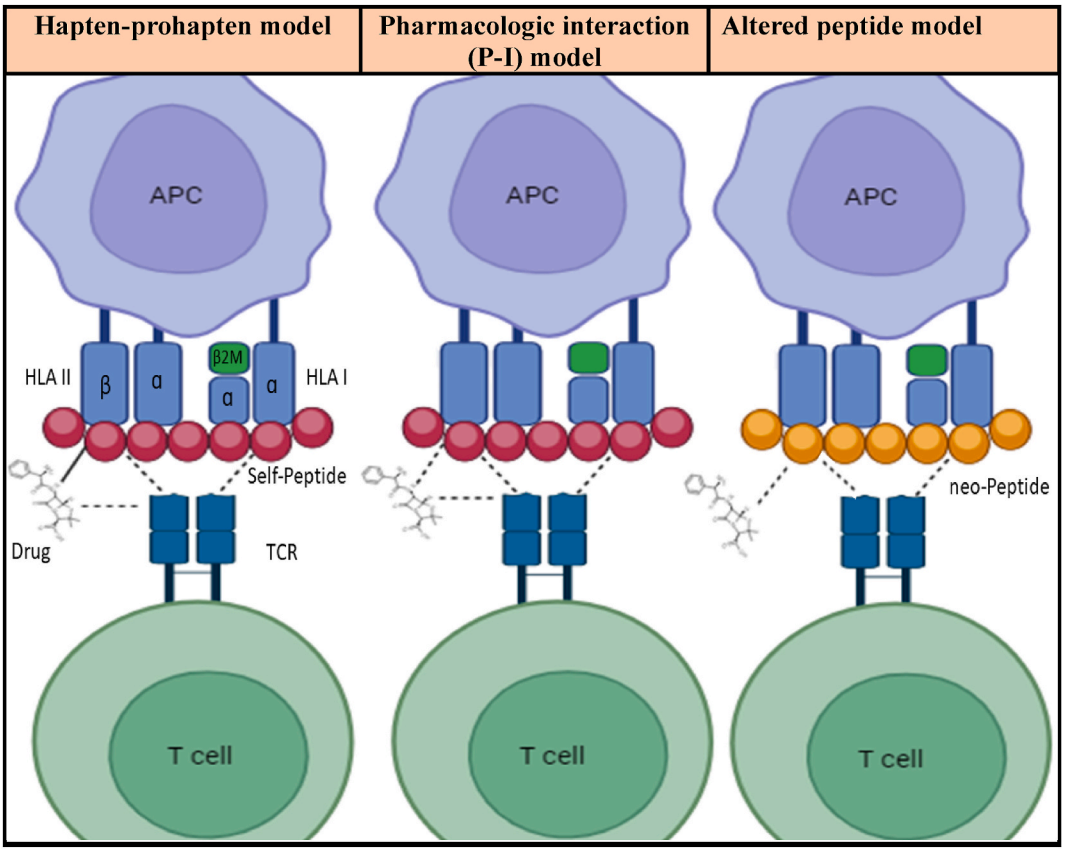

Fig. 2. Mechanisms of T cell–mediated reactions: hapten/prohapten model (left), the pharmacologic interaction (p–i) model (middle), and the altered peptide (right). Covalent bond. Non-covalent bond. APC: Antigen-presenting cell. Adapted with permission from Ref. [31].

a more comprehensive understanding of the immunological pathways underlying the development of DHRs can be achieved [30].

There are four possible mechanisms of drug presentation that hypothesize how small drug antigens may interact with HLA and TCR in DHRs: the hapten theory, the pharmacological interaction with immune receptors (p-i) concept, the altered peptide repertoire model, and the altered TCR repertoire model (Fig. 2). According to the immune pathomechanisms, DHRs have been categorized into three groups: allergic, pharmacological interaction (p-I), and pseudoallergic. Allergic reactions are based on the hapten hypothesis and can be mediated by IgE and IgG antibodies or T-cells. Pharmacological interaction reactions occur when the drug directly binds to human leukocyte antigen (HLA) or T-cell receptor (TCR). Pseudoallergic reactions, on the other hand, involve the drug binding directly to receptors or interacting with enzymes of effector cells, without involving immune mechanisms [11].

1.11. The hapten/pro-hapten model

Haptens are small, chemically reactive compounds (<1000 Da) that bind covalently to proteins or peptides, leading to their modification. This binding can occur in the endoplasmic reticulum (ER) before peptide processing or on the cell surface. The concept of haptens originates from the groundbreaking research of Landsteiner and Jacobs, who were the first to identify a connection between a chemical allergen's reactivity with proteins and its capacity to induce sensitization. The concept of haptens has evolved and extended to cover DHR, especially with the in-depth study of beta-lactam antibiotics. When a hapten binds to a protein, it forms a conjugate, which is then taken up by APCs, like dendritic cells. These cells process the conjugate's antigens and present peptide fragments to the appropriate T cells via MHC molecules. For widely recognized drug haptens such as beta-lactam antibiotics, specific immunogenic epitopes can be identified. Despite this, the precise mechanisms through which these haptens induce immune responses still need further clarification [32]. The ability to form protein adducts is the basis for the hapten/prohapten model of T-cell drug recognition [33].

The hapten model describes IgE-mediated reactions. These reactions occur when a drug, like penicillin, forms a stable covalent bond with a carrier protein, creating a neoantigen that B cells can recognize. This leads to the production of specific IgE antibodies, triggering an immune response. Severe T cell–mediated reactions can result from non-covalent binding of a drug to HLA alleles, which stimulates cytotoxic T cells through their T cell receptors (TCR). While it's still unclear if this T cell activation involves classical antigen presentation of peptides, there is evidence suggesting that high concentrations of extracellular drugs or their metabolites, which are too small to trigger immune responses on their own, can cause non-covalent binding and T cell activation. Further research is needed to understand the exact mechanisms involved in this process [34]. As a result, a culprit drug might attach to certain serum proteins, like albumin. These drug-protein complexes are then processed by APCs, such as dendritic cells, which subsequently present these altered proteins to specific T cells. This process allows T cells to recognize the modified self-proteins and initiate an immune response [35].

Unlike haptens, prohaptens are not chemically reactive and cannot form covalent bonds with peptides. To gain chemical reactivity, prohaptens must undergo metabolic transformation into a compound capable of forming covalent bonds, effectively becoming a hapten. A classic example of prohapten conversion is the hepatic metabolism of sulfamethoxazole by the enzyme CYP2C9, which oxidizes it into sulfamethoxazole-nitroso. This newly formed compound can then bind to proteins within the cell [34]. In Clozapine-induced agranulocytosis, the drug itself acts as a hapten. Diclofenac, together with hepatic proteins, can also form haptens that are recognized by antibodies (type B ADR) [9].

Sulfamethoxazole is not inherently reactive with proteins, but becomes reactive in the liver through a two-step intracellular metabolism process. This process begins with cytochrome P450-dependent reactions, leading to the formation of sulfamethoxazole hydroxylamine. While sulfamethoxazole hydroxylamine doesn't bind to proteins, it can be detected in circulation and eliminated through urine. However, it readily undergoes auto-oxidation in aqueous environments, producing a nitroso intermediate. This intermediate can then alter thiol groups on cellular and serum proteins, creating a variety of chemically diverse antigenic determinants. Hypersensitivity reactions related to sulfamethoxazole mainly impact the skin, with the liver seldom being targeted even though it is exposed to high levels of metabolites. For a prohapten to become an antigen in the skin, skin cells need to produce significant amounts of drug-metabolizing enzymes. Research conducted by Merk (Aachen, Germany) has shown that human skin cells do express considerable levels of certain drug-metabolizing enzymes, providing a basis for why sulfamethoxazole-related hypersensitivity reactions predominantly affect the skin [32].

1.12. The pharmacological interaction model (p-i)

Pichler's "pharmacological interactions of drugs with immune receptors" (p-i concept) presents a new framework for understanding drug-induced immune responses. Unlike the hapten concept, which involves complex and detailed immune responses, the p-i concept suggests that the immune response is primarily limited to T cells, especially preactivated T cells, with a lower activation threshold. In this setting, costimulation may not be required. However, p-i responses can also be heightened by the activation of stress pathways triggered by drugs, bystander cell death caused by drugs, or concurrent viral infections. This framework helps explain why certain drugs can trigger specific T cell responses without the need for traditional hapten-based antigen presentation [32]. The p-i hypothesis suggests that a drug can directly, reversibly, and non-covalently bind to a surface receptor—such as a major histocompatibility complex (MHC) molecule or a T cell receptor—and change its structure. This alteration makes the receptor appear foreign to other adaptive immune system cells, thus triggering an immune response [35]. It does not need antigen processing and drug binding leads to immune complex formation [7].

Recent advancements in their mechanisms have primarily concentrated on identifying novel connections with distinct HLA alleles [36–38]. Nevertheless, it is imperative to consider that in the case of hypersensitivity to anti-retroviral drugs, the response can be

influenced by the viral peptides presented during drug T-cell stimulation [11]. In immunology, a pharmacologically inactive medication that doesn't form covalent bonds with proteins can still have an affinity for certain immune receptors, much like it interacts with other proteins and receptors. In particular circumstances, this reversible interaction between the drug and the receptor can stimulate immune cells that are specific to peptide antigens. As a result, these activated immune cells expand and can lead to various types of inflammatory reactions. Previous research conducted by Wei et al. demonstrated that there is a direct interaction between carbamazepine/aromatic antiepileptic drugs and the HLA-B*15:02 protein. This interaction does not require any intracellular antigen processing or drug metabolism for the presentation of carbamazepine by the HLA-B*15:02 protein [39]. Oxypurinol, which is the metabolite of allopurinol, serves as an additional illustration of the p-i concept. It demonstrates the ability to directly and promptly stimulate drug-specific T cells by selectively utilizing HLA-B*58:01, without the need for intracellular processing [40]. Carbamazepine and some other drugs, as well as nickel, specifically elicit a strong T-cell response without triggering antibody production. This key difference between the p-i concept and the hapten model underlines that while a full immune response involving both T and B cells is typical for many protein antigens, these substances induce a response primarily limited to T cells. This distinction reflects the unique pathway through which these substances can activate immune responses without necessarily engaging the antibody-producing B cells [32]. Numerous drugs, including carbamazepine, allopurinol, and sulfamethoxazole, have demonstrated the ability to be directly acknowledged by the T-cell receptor (TCR) through non-covalent interactions with human leukocyte antigen (HLA) and/or TCR molecules [33].

1.13. Altered peptide repertoire model

The altered peptide repertoire model suggests that certain drugs can non-covalently bind within the peptide-binding cleft of a specific HLA molecule. This interaction changes the cleft's capacity and the array of endogenous peptide ligands it can accommodate, leading to the presentation of new self-peptides that might be perceived as foreign antigens. This, in turn, can trigger an immune response, as these newly presented peptides may activate T cells that recognize them as foreign [7]. The phenomenon of hypersensitivity induced by abacavir has been observed to align with this theoretical framework, as the molecular structure of HLA-B*57:01 has been observed to interact with abacavir and peptides to form complexes [41,42]. These studies have demonstrated that abacavir has a binding affinity for the F-pocket of HLA-B*57:01, leading to structural and chemical modifications in the antigen-binding cleft. Consequently, this alters the range of endogenous peptides and triggers a widespread activation of T cells, resembling an autoimmune-like systemic reaction [40]. In addition, activation of $CD8^+$ clones by flucloxacillin required processing and was limited to HLA-B*57:01* and the closely related *HLA-B*58:01. These clones also showed reactivity to other β-lactam antibiotics such as oxacillin, cloxacillin, and dicloxacillin, but did not react to abacavir or nitroso sulfamethoxazole [27]. A recent study on a mouse model showed that he $CD8^+$ T-cell response to flucloxacillin, dependent on HLA-B*57:01, is constrained by the presence of $CD4^+$ cells, likely regulatory T cells, and the expression of PD-1 [43].

The interaction between a drug and a specific HLA allele can be explained by two main mechanisms: the formation of a haptenated peptide or the non-covalent binding of the drug to the HLA or T cell receptor (TCR), with or without the involvement of an endogenous peptide. However, these models do not fully explain why some patients who carry the specific HLA allele and are exposed to the drug do not develop hypersensitivity, nor do they account for the significant differences in clinical syndromes seen with various drug-HLA allele combinations. These variations might be influenced by other factors, such as genetic predispositions beyond the HLA allele, the patient's immune system state, drug dosage and duration, environmental factors, and concurrent illnesses or infections. Additionally, the precise immune pathways and interactions leading to hypersensitivity are complex and may involve a range of factors beyond the HLA-drug interaction, contributing to the observed variability in drug-induced hypersensitivity reactions [34]. Moreover, abacavir has been introduced as a new allergen by inflammasome-stimulating capacity [44].

1.14. Altered TCR repertoire model

This model indicates that several drugs, such as sulfamethoxazole, can directly interact with TCR, but not with peptides or HLAs. The drug antigens attach to special TCRs and change the conformation of those TCRs, enabling them to bind to HLA-self peptide complexes to initiate immune responses [45]. In this model, TCR is served as an initial drug interaction trigger, proposing that TCRs are as critical as HLAs and contribute to the DHRs. Further, viruses have also been suggested to take part in HLA/drug/TCR interactions such that they may provide exogenous peptides for drug presentation and play important roles in ADR [40]. Although carbamazepine modifies the range of peptides released from HLA-B*15:02, the destruction of carbamazepine-loaded target cells by the carbamazepine-reactive $CD8^+$ T cell lines does not appear to necessitate the presence of peptides. Consequently, carbamazepine may directly interact with the TCR in a manner restricted by HLA-B*15:02 causing carbamazepine-induced SJS in Han Chinese population. This evidence emphasizes the importance of genetic screening and ancestry-specific considerations before prescribing the drug, but only in at-risk populations. The TCR repertoire has been the primary focus of mechanistic investigations in carbamazepine-induced SJS/TEN. $CD8^+$ T cells specific to carbamazepine have been isolated from SJS patients, and in vitro exposure of these cells to carbamazepine has been demonstrated to induce the release of granulysin [34]. It is now suggested that a similar peptide-binding specificity links the risk of HLA-C*04:01-restricted nevirapine hypersensitivity to the HLA-C*18:01 and HLA-C*05:01 alleles, which are common in Hispanic and African populations, respectively. Additionally, a shared E45-L116 motif is recognized as predisposing individuals to methazolamide-induced SJS/TEN among Han Chinese who express HLA-B*59:01 and HLA-B*55:02 [46].

Table 1
New genetic associations of HLA alleles and SNPs with DHRs.

Drug	Clinical manifestation	Allele	Ethnicity/population	Risk Odds Ratio/ prevalence	Ref.
Dapsone and nitroso dapsone	SJS-TEN and DRESS	HLA-B*13:01	Thai and Han-Chinese	54.00	[50]
	SCARs		Thai	9.12	[51]
Phenytoin	DRESS and SCARs	HLA-B*13:01;	Thai	13.29	[52]
		HLA-B*56:02/04,		56.23	
		CYP2C19*3		6.75	
	SCARs	CYP2C9*3 (Reduced activity)	Taiwanese, Japanese, and Malaysian		[53]
	SJS-TEN	HLA-B*15:02	Thai, Han Chinese, Malaysian	5–33	[54, 55]
		HLA-B*15:13	Malaysian	8.56	[55]
Anticonvulsants	SCAR	HLA-A*24:02	Han Chinese	3.15	[56]
Vancomycin	DRESS	HLA-A*32:01	European	19.2 %	[57]
	DILI				
Nevirapine	DILI and SCAR	HLA-B*35:05	Thai	100 %	[58]
		HLA-DRB1*01	White populations		
		HLA-C*04:01	African		[59]
		HLA-C*05:01	Hispanic		[46]
		HLA-C*18:01			
Beta-lactam antibiotics	DILI	HLA-B*48:01 with IR	Thai children	37.4	[57]
		HLA-C*04:06,		23	
		HLA-C*08:01		9.54	
		HLA-DRB1*04:06 with NIR		55	
Flucloxacillin-induced hepatotoxicity and amoxicillin/clavulanic acid		HLA-B*57:01	European	80.6	[55, 60]
		HLA-B*58:01 (only for Flucloxacillin)			
Carbamazepine and oxcarbazepine	SCARs	HLA-B*15:02	Thai	6.63	[51]
			Han Chinese, Indian and other Southeast Asian-ancestries	1–20 %	[19]
	SJS/TEN, DRESS, and Maculopapular rash	HLA-A*31:01	European and Japanese	6.1	[54]
		HLA-B*15:21	Filipino populations		[61]
		correlation between HLA-B*0801 and HLA-DR3, DQ2 and TNF -308	Caucasian	3.2	[62]
	SCARs	HLAB*15:01, HLA-B*15:11,	Han Chinese	potential risk factors	[19]
		HLA-A*02:01, and HLA			
		DRB1*01:01,			
		HLA-A*24:02			
Allopurinol	DRESS	HLA-B*58:01	Han Chinese, Thais, and Southeast Asians	5.25	[51]
		HLA-A*33:03		9.52	
		HLA-Cw*03:02		6.28	
Co-trimoxazole	SCARs	HLA-C*08:01	Thai	8.74	[51]
		HLA-C*06:02		1.64	
		HLA-DRB1*12:02		16.76	
Abacavir	DRESS	HLA-B*57:01	Thai	0.55	
		HLA-B*57:01,	more common in Caucasians		[63]
		HLA-B*58:01, HLA-B*56:02, and			
		HLA-A*31:01			
Raltegravir	DRESS	HLA*B53:01	African		[21,
		HLA*C04:01	Malawian		22]
Zonisamide	SJS/TEN	HLA-A*02:07	Japanese	41.7 %	[64]
Phenobarbital	SJS/TEN	HLA-B*51:01	Japanese	75.0 %	
NSAIDs	NERD	LTC4S expression; LTC4S rs730012	Portuguese	0.98	[65]
	NIUA	ALOX5 rs1132340, rs7220870;	Spanish	0.57,	
		PGE1R rs3810253, rs3810255;		0.77	
		PGER2 rs1254598; PGDR		1.4	
		rs8004654		1.55,	
				1.39	
				1.32	
	NERD	ALOX15 rs3892408	Spanish	3.29	[66]
	NIUA	TBXAS1 rs6962291	Spanish	0.62	[67]
	NERD, NIUA	CEP68 rs75772857	Spanish, Koreans	0.55, 2.63	[68, 69]
	NERD	HLA-DPB1 Met105Val	Korean		[70]
	NERD	Periostin up regulation			[71]
	NERD	CNKSR, SPTBN2	Korean		[72]

(*continued on next page*)

Table 1 (*continued*)

Drug	Clinical manifestation	Allele	Ethnicity/population	Risk Odds Ratio/ prevalence	Ref.
Methazolamide	SJS/TEN	HLA-B*59:01 HLA-B*55:02	Han Chinese, Korean, Japanese Han Chinese	715.3	[33] [46]
Clozapine	agranulocytosis/ granulocytopenia	HLA-DQB1*05:02 HLA-B*39 (158T variant)		0.19 3.3	[73]
Statins	anti-HMGCR myopathy	HLA-DRB1*11:01	whites and African Americans	10.4	[74]
Lumiracoxib	DILI	HLA haplotype (HLA-DRB1*15:01-HLA-DQB1*06:02-HLA-DRB5*01:01-HLA-DQA1*01:02)		5.0	[75]
Co-amoxiclav	DILI	HLA-DRB1*15:01-DQB1*06:02	European and US cases		[76]
Lapatinib	DILI	HLA-DQA1*02:01 HLA- DRB1*07:01			[77, 78]
Ticlopidine	DILI	HLA-A*33:03 HLA-DQB1*06:04			[59]
Ximelagatran	DILI	HLA- DRB1*07:01 HLA-DQB1*02:01			
Asparaginase		HLA-DRB1*07:01 HLA-DQB1*02:02 DQA1*02:01	Hungarian and European	2.86 2.99	
Clometacin	DILI	HLA-DQB1*02:01			
Lamotrigine	SCAR	HLAs-B*5801, A*6801, Cw*0718, DQB1*0609, and DRB1*1301	Caucasian (W, EU)		[79]
	SJS/TEN	HLA-B*15:02	Han Chinese in Taiwan, Hong Kong, Thais and Indians	15 %	[19]
Eslicarbazepine acetate	SJS/TEN	HLA-B*15:02			[54]
Aspirin	AICU	HLA- DRB1*13:02, HLA-DQB1*06:09, HLA-DPB1*02:01 haplotype	Korean		[80]
	AERD	HLA-DPB1*03:01	Korean		[81]
Trichloroethylene	OTHS	HLA-B*13:01	Chinese	83.3 %	[82]
Minocycline	pulmonary involvement in DRESS	HLA	Japanese, Caribbean blacks		[63]
Enalapril, erythromycin, fenofibrate, methyldopa, sertraline, terbinafine, and Ticlopidine	DILI	HLA-A*33:01	European ancestry	2.7	[83]
Flupirtine	DILI	HLA-DRB1*16:01-DQB1*05:02	European	18.7	[84]
Irinotecan	DIA	UGT1A1 variant			[3]
Antithyroid drugs (thiamazole [Methimazole], carbimazole, or propylthiouracil)	DIA	HLA-B*38:02 and HLA-DRB1*08:03, HLA-B*27:05 and other SNPs on chr 6	Chinese people in Taiwan and Hong Kong, white European		[85]

Abbreviations: Aspirin-Exacerbated Respiratory Disease (AERD); drug-induced agranulocytosis (DIA); Drug-induced liver injury (DILI); Drug reaction with eosinophilia and systemic symptoms (DRESS); NSAID-exacerbated respiratory disease (NERD); Occupational Trichloroethylene Hypersensitivity Syndrome (OTHS); Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS-TEN).

1.15. The role of genetics in DHRs

Based on genome-wide association studies (GWAS), DHRs can be strongly dependent on the genetic susceptibility of the host. Recently, the results of the investigations can be greatly expanded by some novel techniques, including next-generation sequencing (NGS). Some pioneering studies provided novel information in this realm and 16 genes of the Vitamin D pathway and the high-affinity IgE receptor were recognized in relation to allergic diseases and DHRs [47]. Furthermore, strong relationships between genetic markers on pharmacokinetics have been reported for type B DHRs [48,49].

Additional risk factors for DHRs include being of white race, female gender, having systemic mastocytosis, and asthma. Furthermore, individuals with diabetes, chronic urticaria, and drug allergies are at an increased risk of experiencing reactions to radiocontrast media (RCM). The higher prevalence of DHRs in females can be attributed to factors such as greater drug consumption, genetic predisposition, epigenetic changes, and hormonal interactions with immune cells. Age, particularly among the elderly, has also been identified as a significant factor, with DHRs becoming more prevalent and severe, likely due to the presence of comorbidities and the use of multiple medications. Consequently, strategies aimed at reducing inappropriate prescriptions are necessary to minimize the incidence of DHRs in this population. Additionally, recent research has uncovered new genetic associations with DHRs [11] which are summarized in Table 1.

Human leukocyte antigen (HLA) gene polymorphisms may be involved in penicillin-induced immediate hypersensitivity reactions. It has been shown that some HLA genes residing on chromosome 6 are strongly linked with type IV ADR [49]. The relationship between DHRs and HLA alleles has been a prominent area of research, primarily due to the significant impact observed, and remains an ongoing

topic of investigation. Interestingly, it has been observed that not all individuals carrying risk alleles associated with hypersensitivity exhibit symptoms. A study conducted by Hung and Chen in Taiwan, who initially identified the association between HLA-B*1502 and carbamazepine-induced Stevens-Johnson syndrome (SJS), addressed this issue. They investigated the activation of specific T-cell receptor Vβs (e.g., TCRVb11) and the utilization of particular clonotypes in HLA-B*1502-positive individuals. Their findings revealed a significant association between these TCR phenotypes and the reaction to carbamazepine in vitro, exclusively in patients expressing this TCR phenotype. Conversely, carbamazepine-tolerant individuals did not possess these TCRs. Furthermore, the researchers were able to induce a primary immune response in healthy HLA-B*1502 individuals who had the corresponding TCR clonotype present in their circulation. Based on these results, they concluded that they had identified the missing link between HLA-B*1502-positive tolerant and diseased individuals [32]. A recent GWAS study revealed that HLA-DRB1*15:01 might be associated with alcohol-induced liver cirrhosis [86]. The response of T cells was restricted by HLA class II, with amoxicillin-altered peptides specifically binding to HLA-DRB1*15:01 and/or DQB1*06:02. Amoxicillin-modified peptides engage with both elements of the risk haplotype to activate T cells in DILI patients and highlight the significance of the placement of the nucleophilic lysine residue within the peptide sequence that binds to HLA [87].

It is noteworthy that investigations indicated that some drugs, such as penicillins and sulfonamides, are not associated with HLA alleles. Possibly, they form several epitopes and interact with several HLA alleles. Other possible reasons may be that studies have not evaluated mixed phenotypes and small sample sizes. A previous GWAS study in which phenotyping was conducted on a reasonable sample size with penicillin-induced type 1 IgE-mediated reactions demonstrated an association with the HLA-DRA region [88]. A functional study conducted on a carbamazepine-hypersensitive case indicated that activation of both HLA-A*31:01–restricted, carbamazepine-specific $CD8^+$ T cells in Chinese population and HLA-DRB1*04:04–restricted, carbamazepine-specific $CD4^+$ T cells is associated with discrete T cell phenotypes within the extended genetic haplotype, affecting the clinical manifestations in different patients [89].

1.16. Metabolic SNPs

Many disease predispositions are associated with single nucleotide polymorphisms (SNPs) in important genes involved in immune regulation, metabolism, and cytokine signaling. However, the identification of these SNPs through genome-wide association studies (GWAS) is limited, suggesting that their impact on disease susceptibility is likely to be smaller compared to that of HLA alleles [90]. Metabolic single nucleotide polymorphisms (SNPs) may not only influence the speed at which the culprit antigen is produced or eliminated, but also the extent of "danger signaling." In cases where higher concentrations of these antigens are present, indicating greater tissue damage, more potent signals are generated that have the ability to direct the immune system's response. In various ethnicities, SNPs in some related genes and promoter variants in candidate genes involved in specific antibody production are the most focused issue in the field of the genetics of DHRs [91]. Several metabolic associations have been identified, with one notable example being CYP2C9*3. This particular association is characterized by a significant reduction in metabolizing capacity, up to 95 %, which subsequently increases the risk of serious cutaneous adverse reactions when using the anticonvulsant phenytoin. IgE/IL4-IL13 axis as an important therapeutic signaling pathway in allergic diseases is the most studied mechanisms in allergic reactions to drugs. In an Italian population, two SNPs in IL13 ($-1055C > T$ and R130Q) and 2 SNPs in the IL4 receptor genes (IL4RA, I50V, and Q551R) were introduced for immediate reactions to β-lactam antibiotics [92].

In recent years, a number of studies have documented a substitution of His645Asp in diamino oxidase (+8956C/G), which leads to a diminished ability to metabolize histamine in the bloodstream. Consequently, this results in elevated and prolonged levels of histamine, increasing the risk of immediate reactions to nonsteroidal anti-inflammatory drugs (NSAIDs). Despite the available evidence and the observed correlation between higher drug dosages and cutaneous reactions, only a limited number of studies have explored the association between single nucleotide polymorphisms (SNPs) in metabolic enzymes and transporters and DHRs. This may be attributed to the fractional clearance of the drug. If drug clearance is reliant on a specific pathway, any variations in that pathway are more likely to predispose individuals to ADRs [90]. The cytochrome P450 (CYP) enzymes play a crucial role in the metabolism of both endogenous and exogenous substances, particularly in drug metabolism. A recent genome-wide association study (GWAS) was conducted to investigate severe cutaneous adverse reactions (SCARs) in individuals from Taiwan, Japan, and Malaysia who had used phenytoin. The study focused on identifying single nucleotide polymorphisms (SNPs) within the CYP2C gene, which codes for a hepatic enzyme responsible for metabolizing phenytoin. The study found 16 SNPs within this gene, with one specific variant, CYP2C9*3, showing a significant association with the development of SCARs. This variant was found to decrease the clearance of phenytoin, leading to higher concentrations of the drug in the bloodstream [93]. The presence of the allele CYP2C9*3 has been associated with reduced clearance of phenytoin. However, it is important to note that reduced phenytoin clearance has also been observed in patients who do not carry this allele. This suggests that other factors, such as liver or renal function, may also play a role in the development of phenytoin-induced severe cutaneous adverse reactions (SCARs). Similarly, a genetic association has been reported between reduced nevirapine clearance and allelic variants of CYP2B6 G516T and T983C. Carriers of these variants are at a higher risk of developing nevirapine-induced SJS/TEN, while individuals with the wild-type genotype for both single nucleotide polymorphisms (SNPs) exhibit a protective effect [94]. The absence of the glutathione transferase GSTM1 phenotype was found to have a limited correlation with the susceptibility to SJS/TEN in patients who were administered nevirapine [95]. A novel bioinformatics analysis of genome-wide association study (GWAS) findings unveiled a notable enrichment of genetic variants associated with SJS/TEN within the ABC transporter pathway. A previous study in Taiwan revealed several SNPs, including rs3130690, rs2848716, rs750332, that are associated with carbamazepine hypersensitivity [96].

1.17. Emerging role of epigenetics

The immune regulatory network is influenced not only by genetic variation but also by epigenetic factors derived from the environment. Obtaining a comprehensive record of antigenic exposure history is unfeasible, but it may be possible to identify specific methylation patterns that regulate the expression of genes involved in immune regulation. Furthermore, emerging evidence suggests that while the immune status is influenced by the individual's environmental exposure history, exposures experienced by parents and grandparents may also play a significant role. Therefore, it is crucial to define the exposome that alters the immune response towards activation in order to gain insights into the predisposition to drug hypersensitivity reactions [90].

In the past decade, several studies have revealed a correlation between epigenetic modifications and expression levels or activity of genes involved in drug absorption, distribution, metabolism and excretion (ADME) and pharmacodynamics [97]. Notable instances of such connections can be observed in the associations between DNA methylation in the promoters of CYP3A4, CYP1A2, CYP2C19, and UGT1A1 genes, and the corresponding levels of gene expression [98,99]. In previous studies conducted on hepatic cell lines (HepG2), it has been demonstrated that the transcriptional activation of CYP3A4 is dependent on the presence of the histone methyl transferase PRMT1. This was evidenced by a significant decrease in the activation of CYP3A4 by rifampicin, reaching a reduction of 20-fold, following the knock-down of PRMT1 [100]. Moreover, the activation of PXR leads to the upregulation of CYP3A4 through the administration of rifampicin, which subsequently causes alterations in the histone profile. These changes include elevated levels of H3K4me3 and H3ac, along with reduced levels of the repressive histone mark H3K27me3 [101]. Significantly, the aforementioned alterations are a direct result of the activation of transcription, as demonstrated by the inhibition of PXR leading to the prevention of both transcriptional activation and epigenetic modifications. Furthermore, it has been observed that the patterns of histone modifications are closely associated with the expression levels of various drug transporters, including ABCB1 (MDR1) and ABCG2 (BCRP) [102]. The promoters of several CYP genes, such as CYP1A1, CYP1B1, CYP2D6, and CYP2E1, exhibit hypermethylation in hepatocyte-like cells derived from embryonic stem cells. This hypermethylation is associated with a significant decrease in the expression of these genes, reaching multiple orders of magnitude lower levels compared to primary human hepatocyte cultures. Notably, when DNA methyltransferases (DNMTs) and histone deacetylases (HDACs) were pharmacologically inhibited, the expression of CYP1A1 and CYP1B1 increased by 10-fold. However, the changes in CYP2D6 and CYP2E1 expression were not as pronounced [103]. These findings offer empirical support for the direct association between epigenetic modifications and the expression levels of ADME genes. Notably, epigenetic alterations in ADME genes exhibit a strong correlation with expression patterns during the developmental stages of embryos. Specifically, the dominant isoform of CYP3A in the liver of embryos is CYP3A7, whereas postnatal stages witness a transition to CYP3A4. This transition is accompanied by changes in the methylation levels of transcription factor binding sites within the promoters of CYP3A genes in both mice and humans In colon cancer cells and their metastases, there is a notable decrease in methylation levels at a significant CpG island located at the junction between exon 1 and intron 1. This hypomethylation leads to the reactivation of CYP2W1 expression. Given that this enzyme has the ability to activate anticancer prodrugs, its selective expression in cancer cells presents a promising avenue for the development of novel anticancer drugs [104]. Interestingly 5-hydroxymethylcytosine (5-hmC) has been shown as a relatively stable epigenetic marker helpful in specifying transcriptionally active regions and robust clinical epigenetic variations [105]. Significantly, there is a substantial difference in global hydroxymethylation levels between human livers, with a four-fold variation. Our findings demonstrate a positive association between hydroxymethylation in coding regions and the expression levels of corresponding human ADME genes. These results suggest that the variability in hydroxymethylation plays a role in the epigenetic regulation of hepatic gene expression, potentially through inducing chromatin modifications that facilitate gene transcription. It is worth noting that epigenomic profiles exhibit a high degree of tissue specificity, with each cell type possessing its distinct signature. Furthermore, correlations between the epigenomes of different tissues, particularly blood, are generally weak [106]. However, the majority of studies investigating epigenetic associations rely on peripheral blood as a substitute for the target tissue. Therefore, we reiterate our previous concerns that accurate conclusions regarding epigenetic regulation necessitate the analysis of meticulously isolated biopsy samples from the specific tissue of interest in order to account for its unique characteristics [107].

2. Conclusion

DHRs are very complicated and challenging. Some obstacles in the understanding of the etiology and immunopathogenesis of DHRs, slow down the development of effective diagnostic and prognostic tests or tools. The interplay between immune cells, particularly T cells, and predisposing genes delineates the type, severity, and underlying mechanisms of DHRs. To this end, immunogenetic studies such as HLA-typing, SNPs in genes and promoters related to metabolizing enzymes, and epigenetic factors are potential markers for predicting potential DHRs. Correspondingly, the risk of developing DHRs may prominently be reduced before drug administration. However, the association of HLAs, metabolic SNPs, and epigenetic factors with DHRs needs further investigation. Moreover, the type and severity of immune response and pattern of immune cells infiltrated into the damaged tissue may predict possible responses in susceptible individuals or specify the prognosis of treatment in inflicted subjects. Large-scale multicentric studies are needed to find promising novel in vitro or *in vivo* diagnostic and prognostic markers for identifying susceptible subjects or providing treatment protocols to work up patients with drug allergies as personalized medicine because drug provocations may be life-threatening in such patients. In addition, allergic cards or drug allergy passports are strongly suggested, which contain necessary information on the culprit drug(s), clinical manifestations upon consumption, including severity, potential cross-reactivity, alternative drugs to prescribe, and where more detailed information is accessible. However, electronic prescription systems will become more prevalent in the future.

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Rasol Molatefi: Conceptualization. **Sedighe Talebi:** Writing – original draft, Conceptualization. **Azam Samei:** Investigation. **Neda Roshanravan:** Investigation, Conceptualization. **Shirin Manshouri:** Investigation. **Baran Hashemi:** Investigation. **Vahid Ghobadi Dana:** Conceptualization. **Erfan Mosharkesh:** Visualization. **Mohammad Ali Bahar:** Investigation. **Sholeh Khajoei:** Writing – original draft, Investigation. **Farhad Seif:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

Antibody-dependent cell-mediated cytotoxicity (ADCC)
Adverse Drug Reactions (ADRs)
Aspirin-Exacerbated Respiratory Disease (AERD)
Acute generalized exanthematic pustulosis (AGEP)
antigen-presenting cells (APCs)
body surface area (BSA)
drug-induced agranulocytosis (DIA)
Drug-induced liver injury (DILI)
Drug-induced renal injury (DIRI)
drug reaction with eosinophilia and systemic symptoms (DRESS)
granulocyte-macrophage colony-stimulating factor (GM-CSF)
Human Leukocyte Antigens (HLAs)
Interleukin (IL)
Interferon-gamma (IFN-γ)
NSAID-exacerbated respiratory disease (NERD)
nonsteroidal anti-inflammatory drugs (NSAIDs)
Occupational Trichloroethylene Hypersensitivity Syndrome (OTHS)
pharmacological interaction (pi)
Severe Cutaneous Adverse Reactions (SCARs)
specific IgE (sIgE)
Stevens-Johnson syndrome (SJS)
single-nucleotide polymorphisms (SNPs)
T cell receptors (TCRs)
Toxic epidermal necrolysis (TEN)
tumor necrosis factor (TNF-α)

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