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Evolving models of the immunopathogenesis of T cell–mediated drug allergy: The role of host, pathogens, and drug response

Katie D. White, MD, PhD,[a] Wen-Hung Chung, MD, PhD,[b,c,d] Shuen-Iu Hung, PhD,[e] Simon Mallal, MBBS, FRACP, FRCPA,[a,f] and Elizabeth J. Phillips, MD, FRCPC, FRACP[a,f] *Nashville, Tenn, Keelung, Linkou, Taoyuan, and Taipei, Taiwan, and Murdoch, Australia*

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Activity Objectives:

1. To understand the role of host genetics, microbes, and drugs in the development of immune-mediated (IM) adverse drug reactions (ADRs).
2. To understand the existing models and proposed heterologous immunity model in the pathogenesis of IM-ADRs.
3. To understand the importance of genetic screening before drug administration in selected high-risk populations to prevent ADRs.

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List of CME Exam Authors: Karen Tuano, MD, Qurat Kamili, MD, Shuya Wu, MD, PhD, Sana Hasan, MD, Atoosa Kourosh, MD, MPH, Kwei Akuete, MD, MPH, Evan Li, MD, Rachel Jones, Larraine Lyter-Reed, NP, Teddi Thornhill, MD, Mehtap Abul, MD, Lenora Noroski, MD, MPH, and William T. Shearer, MD, PhD.

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Immune-mediated (IM) adverse drug reactions (ADRs) are an underrecognized source of preventable morbidity, mortality, and cost. Increasingly, genetic variation in the HLA loci is associated with risk of severe reactions, highlighting the importance of T-cell immune responses in the mechanisms of both B cell–mediated and primary T cell–mediated IM-ADRs. In this review we summarize the role of host genetics, microbes, and drugs in IM-ADR development; expand on the existing models of IM-ADR pathogenesis to address multiple unexplained observations; discuss the implications of this work in clinical practice today; and describe future applications for preclinical drug toxicity screening, drug design, and development. (J Allergy Clin Immunol 2015;136:219-34.)

Key words: *Abacavir, adverse drug reaction, allopurinol, altered peptide, carbamazepine, drug reaction with eosinophilia and systemic symptoms, hapten, heterologous immunity, human herpesvirus, human leukocyte antigen, major histocompatibility complex, p-i, pharmacogenetics, pharmacogenomics, Stevens-Johnson syndrome, T-cell receptor, toxic epidermal necrolysis*

From [a]the Department of Medicine, Vanderbilt University Medical Center, Nashville; [b]the Department of Dermatology, Chang Gung Memorial Hospital, Keelung; [c]the Department of Dermatology, Drug Hypersensitivity Clinical and Research Center, Chang Gung Memorial Hospital, Linkou; [d]the College of Medicine, Chang Gung University, Taoyuan; [e]the Program in Molecular Medicine, Institute of Pharmacology, School of Medicine, Infection and Immunity Research Center, National Yang-Ming University, Taipei; and [f]the Institute for Immunology and Infectious Diseases, Murdoch University.

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Corresponding author: Elizabeth J. Phillips, MD, FRCPC, FRACP, A-2200, Medical Center North, Division of Infectious Diseases, Vanderbilt University Medical Center, Nashville, TN 37232-2582. E-mail: elizabeth.j.phillips@vanderbilt.edu.

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Abbreviations used

ADR: Adverse drug reaction
APC: Antigen-presenting cell
CDR: Complementarity-determining region
CMV: Cytomegalovirus
DRESS: Drug reaction with eosinophilia and systemic symptoms
FDA: US Food and Drug Administration
HHV: Human herpesvirus
HSV: Herpes simplex virus
IM: Immune mediated
OR: Odds ratio
p-i: Pharmacologic interaction
PREDICT-1: Prospective Randomized Evaluation of DNA Screening in a Clinical Trial
SHAPE: Study of Hypersensitivity to Abacavir and Pharmacogenetic Evaluation Study Team
SJS: Stevens-Johnson syndrome
TCR: T-cell receptor
T_{EM}: Effector memory T
TEN: Toxic epidermal necrolysis
VZV: Varicella zoster virus

Adverse drug reactions (ADRs) are sources of major burden to patients and the health care system, and 50% of such reactions are preventable.[1-8] The majority of ADRs are predictable based on the on-target pharmacologic activity of the drug (Fig 1).[2,4-7,9,10] Up to 20% of all ADRs are not readily anticipated based on pharmacologic principles alone and, until recently, were considered "idiopathic" and "unpredictable." We now know that these reactions stem from specific off-target drug activity and include the immune-mediated (IM) ADRs, as well as off-target pharmacologic drug effects, such as those seen in patients with non–IgE-mediated mast cell activation syndrome (Fig 1).[11] IM-ADRs encompass a number of phenotypically distinct clinical diagnoses that comprise both B cell–mediated (antibody-mediated, Gell-Coombs types I-III) and purely T cell–mediated (Gell-Coombs type IV) reactions. The clinically relevant T cell–mediated drug reactions have been classified into delayed exanthema without systemic symptoms (maculopapular eruption), contact dermatitis, drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DRESS)/hypersensitivity syndrome, Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis, fixed drug eruption, and single organ involvement pathologies, such as drug-induced liver injury and pancreatitis. Allelic variation in the genes that encode the MHC family of proteins is often associated with risk of T cell–mediated drug hypersensitivity reactions in certain populations (Table I).[12-69]

This review focuses on the purely T cell–mediated drug hypersensitivity reactions, although the same principles and models likely apply to B cell–mediated reactions as well.[12,70,71] Here we provide an overview of the data supporting current models of T cell–mediated drug hypersensitivity reactions, propose a new model of drug hypersensitivity that expands on the existing models to include the role of microbial pathogen exposure in the generation of drug-specific T-cell responses, and discuss the implications for clinical practice and drug safety, design, and development.

OVERVIEW OF THE T-CELL IMMUNE RESPONSE, THE αβ T-CELL RECEPTOR, AND MHC

During maturation in the thymus, developing T cells undergo the sequential processes of positive and negative selection to generate a functional repertoire composed of a subject-specific, HLA-restricted subset of the total possible repertoire encoded by the T-cell receptor (TCR) genes. Engagement of the TCR by the appropriate peptide-MHC ligand results in T-cell clonal proliferation and differentiation into effector and memory phenotypes (Fig 2, *A*). A subset of the memory population, termed effector memory T (T_{EM}) cells, is characterized by the expression of the cellular marker CD45RO and lack of expression of the lymph node homing receptor CCR7.[72] This allows these cells to maintain surveillance in the tissue site of the initial antigen encounter, which is often the site of pathogen re-exposure. Because these cells require fewer costimulatory signals for activation and retain the ability to secrete proinflammatory cytokines (TNF-α, IL-2, and IFN-γ) and cytotoxic peptides, they are equipped and poised at strategic anatomic sites to initiate a swift immune response at reencounter with pathogen-specific antigens.[72-79] Contact with peptide-MHC is mediated by the αβ TCR, which is composed of 2 polypeptide chains that each contain a variable region (V_α and V_β). The distal residues of these variable sequences comprise 6 complementarity-determining regions (CDRs) that engage peptide-MHC on the surface of the target cell. The CDR1 and CDR2 loops mediate contact with the MHC binding groove α-helices, whereas the CDR3 loops mediate the majority of peptide contacts and thus display the greatest degree of sequence variability in the TCR gene.[80] The majority of MHC sequence diversity is found among amino acids in the binding groove that mediate peptide binding to the MHC. This polymorphism is presumably the legacy of selection pressure to confer immunity against a myriad of infectious pathogens.[81,82] Subjects who are heterozygous at the HLA loci will express a more diverse array of MHC proteins, thereby increasing the diversity of peptides presented to T cells. Theoretically, this will increase the probability that a pathogen will be recognized and elicit an immune response.[83-87]

IMMUNOPATHOGENESIS OF DRUG HYPERSENSITIVITY: ESTABLISHED MODELS

The role of T cell–mediated immune responses in the pathogenesis of many IM-ADRs has been firmly established. However, the specific molecular mechanisms that underpin these reactions have been elucidated in only a handful of cases. This is in contrast to the numerous reported associations among HLA alleles and drug-specific hypersensitivity reactions (reviewed in White et al[88] and Pavlos et al[12]). Three nonmutually exclusive models that describe how a small-molecule pharmaceutical might elicit T-cell reactivity have been developed, namely the hapten/prohapten model, the pharmacologic interaction (p-i) model, and the altered peptide repertoire model (Fig 2, *B*).

In the hapten/prohapten model the offending drug or a reactive metabolite of the drug binds covalently to an endogenous protein that then undergoes intracellular processing to generate a pool of chemically modified peptides. When presented in the context of MHC, these modified peptides will be recognized as "foreign" by T cells and elicit an immune response that might also include a B cell–mediated antibody response.[89-92] Examples of IM-ADRs that are associated with hapten modification of endogenous proteins include the binding of penicillin derivatives to serum