

Molecular mechanisms of CD8+ T cell-mediated delayed hypersensitivity: Implications for allergies, asthma, and autoimmunity

Richard S. Kalish, MD, PhD,^a and Philip W. Askenase, MD^b Stony Brook, NY, and New Haven, Conn

Delayed-type hypersensitivity (DTH) is defined as the recruitment of T cells into tissues to be activated by antigen-presenting cells to produce cytokines that mediate local inflammation. CD8+ T cells are now known to mediate DTH responses in allergic contact dermatitis, drug eruptions, asthma, and autoimmune diseases. This inflammatory effector capability of CD8+ cytotoxic T cells was previously poorly recognized, but there is now considerable evidence that these diseases may be mediated by CD8+ DTH. The difference between CD8+ T cells and CD4+ T cells mediating DTH relates to the molecular mechanisms by which antigens are processed and presented to the T cells. Antigens external to the cell are phagocytosed and processed for presentation on MHC class II molecules (eg, HLA-DR) to CD4+ T cells. In contrast, internal cytoplasmic antigens are processed by the endogenous pathway for presentation on MHC class I molecules (eg, HLA-A, -B, and -C) to CD8+ T cells. External allergens can also enter the endogenous pathway to be presented to CD8+ T cells. These include many contact sensitizers, chemical and protein respiratory allergens, viral antigens, metabolic products of drugs, and autoantigens. The resulting CD8+ T-cell response explains the role of CD8+ T-cell DTH mechanisms in allergic contact dermatitis, asthma, drug eruptions, and autoimmune diseases. (J Allergy Clin Immunol 1999;103:192-9.)

Key words: T lymphocytes, CD8+, delayed hypersensitivity, allergic contact dermatitis, drug eruptions, asthma

Delayed-type hypersensitivity (DTH) is epitomized by the tuberculin reaction but also includes allergic contact

Abbreviations used

ACD:	Allergic contact dermatitis
APC:	Antigen presenting cell
DNCB:	Dinitrochlorobenzene
DNFB:	Dinitrofluorobenzene
DTH:	Delayed-type hypersensitivity
TCR:	T-cell receptor
TNCB:	Trinitrochlorobenzene

dermatitis (ACD), as well as a variety of delayed time course immune inflammatory responses in various tissues. Although DTH responses often are mediated by CD4+ T cells, it now is clear that CD8+ T cells are in fact also responsible for DTH responses, many of which are clinically relevant. It is this newly recognized participation of CD8+ T cells in DTH that is the focus of our discussion.

CD8+ AND CD4+ T CELLS: SIMILARITIES AND DIFFERENCES RELEVANT TO DTH

CD8+ and CD4+ T cells are now recognized to have similar capabilities (Table I). Formerly it was held that only CD4+ T cells mediate DTH responses, but it has recently been shown in several systems that both CD8+ and CD4+ T cells can mediate DTH. Both T-cell subsets can be cytotoxic by using overlapping mechanisms.^{1,2} In addition, both subsets proliferate and can produce similar patterns of T_{H1} and T_{H2} cytokines when challenged with antigen. The major qualitative difference between CD4+ and CD8+ T cells is that CD4+ T cells recognize antigens presented by class II MHC molecules (eg, HLA-DR, -DP, and -DQ in humans), whereas CD8+ T cells recognize antigens presented by class I MHC molecules (eg, HLA-A, -B, and -C). In addition, CD4+ T cells tend to produce higher levels of some cytokines, particularly those needed as helper factors to stimulate production of antibodies, such as IL-4 and IL-5, by B cells. Thus the

From ^athe Department of Dermatology, State University of New York at Stony Brook Health Sciences Center, Stony Brook; and ^bYale University School of Medicine, New Haven.

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Reprint requests: Richard S. Kalish, MD, PhD, Department of Dermatology, SUNY at Stony Brook Health Sciences Center, Stony Brook, NY 11794-8165.

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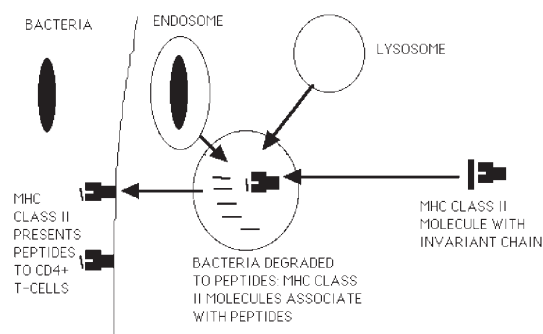


FIG 1. Processing and presentation of exogenous antigens.

TABLE I. CD8+ and CD4+ T cells

Property	CD4+ cells	CD8+ cells
Antigen recognition	MHC class II	MHC class I
Source of antigens	Extracellular	Cytoplasm
Antigen processing	Exogenous	Endogenous
Cytotoxic	Yes: MHC class II	YES: MHC class I
Cytokines	T _{H1} and T _{H2}	Tc1 and Tc2
Participate in DTH	Yes	Yes

former distinction of CD4+ “helper T cells” versus CD8+ “suppressor/cytotoxic” T cells is now inadequate.

As noted above, the critical distinction between CD4+ and CD8+ T cells pertains to recognition of antigens presented by different MHC molecules. The mode of antigen presentation is in turn dependent on the molecular mechanisms of processing of the antigens by degradation pathways inside of the antigen-presenting cells (APCs).

Protein antigens must be processed into small peptides by the APCs (eg, dendritic cells, macrophages, and monocytes) before their presentation to T cells as peptides bound in the MHC molecules.^{3,4} This metabolism-dependent intracellular processing involves degradation of proteins into peptide fragments, which subsequently are presented on the surface of the APCs and bound to MHC molecules.

PROCESSING OF EXOGENOUS ANTIGENS FOR PRESENTATION BY MHC CLASS II MOLECULES TO CD4+ T CELLS

Protein antigens that arise outside of the APCs (exogenous antigens) are processed by the “exogenous pathway” for presentation to T cells (Fig 1).⁵ Such exogenous proteins are preferentially presented on MHC class II molecules (eg, HLA-DR) for recognition by CD4+ cells.⁶ Examples of exogenous antigens include extracellular bacteria, bacterial toxins, fungal antigens, vaccines, and allergens such as pollens and house dust mite. Exogenous proteins are internalized into APCs by phagocytosis or pinocytosis and subsequently localize in endosomal vacuoles, which fuse with lysosomes. Intracellular

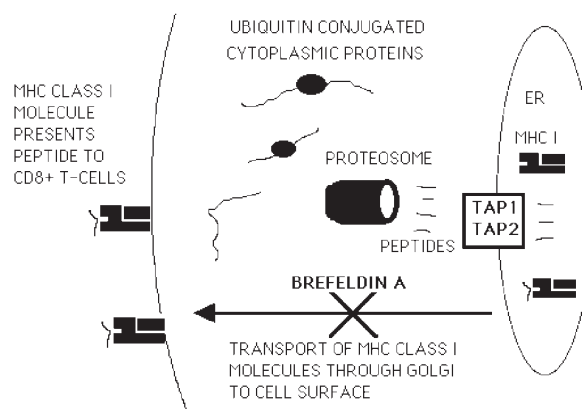


FIG 2. Processing and presentation of endogenous antigens.

lysosomes have an acidic pH⁷ and contain multiple degradative enzymes, such as acid proteases and cathepsins.^{8,9} Exogenous antigens are degraded into peptides in this endosome/lysosome compartment.

MHC class II molecules are synthesized in the endoplasmic reticulum and transported to the endosome compartment bound to a protein termed the “invariant chain.”¹⁰ The invariant chain acts as a chaperone to block the peptide-binding site of MHC class II molecules, preventing the binding of intracellular peptides to the class II molecules before arrival in the endosome/lysosome compartment.¹¹ By this mechanism, MHC class II molecules are prevented from binding peptides in the endoplasmic reticulum. In the endosome/lysosome compartment, the nascent MHC class II molecules are released from the invariant chain and bind to processed peptides.¹² Endosome-derived peptides are subsequently transported to the cell surface for presentation by MHC class II molecules and recognition by specific α/β T-cell receptors (TCRs) on CD4+ T cells.

PROCESSING OF ENDOGENOUS ANTIGENS FOR SUBSEQUENT PRESENTATION BY MHC CLASS I MOLECULES TO CD8+ T CELLS

Protein antigens that arise within the cell (endogenously synthesized antigens) are processed in the “endogenous pathway” for presentation to T cells (Fig 2).¹³ Examples of endogenous antigens include transplantation antigens, viral antigens, and tumor-associated antigens. Endogenous proteins, after processing into peptides, preferentially complex with MHC class I molecules (eg, HLA-A, -B, and -C) for transport to the cell surface and presentation by MHC class I molecules to specific α/β TCRs on the surface of CD8+ T cells.¹⁴

Endogenous antigens are derived from cytoplasmic proteins that are degraded into peptides by the intracellular proteasome complex.¹⁵ Denatured cytoplasmic proteins are conjugated with ubiquitin and targeted for proteolysis by the proteasome complex. This large multi-

subunit particle contains several proteolytic activities that preferentially generate peptides of 8 to 10 amino acids in length, which is the ideal length for binding to MHC class I molecules.¹⁶ These peptides are transported into the endoplasmic reticulum for binding to MHC class I molecules.¹⁷ Transport of peptides from the cytoplasm to the endoplasmic reticulum is a function of the TAP-1 and TAP-2 gene products.¹⁸ Although it has not been proven directly that TAP-1 and TAP-2 proteins transport the peptides, mutations or deletions of these genes interfere with the delivery of cytoplasmic peptides to the MHC class I molecules.

Peptides generated by the proteasome complex associate with newly synthesized MHC class I molecules in the endoplasmic reticulum. The MHC class I molecules, along with bound peptides, are transported from the endoplasmic reticulum through the Golgi apparatus to the cell surface, where they are eventually presented to CD8⁺ T cells.¹⁹ By this pathway, antigens derived from cytoplasmic proteins are presented by MHC class I molecules to CD8⁺ T cells.

DIVISION OF THE IMMUNE RESPONSE BY ANTIGEN-PROCESSING PATHWAYS HAS FUNCTIONAL SIGNIFICANCE FOR CD4⁺ AND CD8⁺ T CELL-MEDIATED DTH

Separation of antigen processing into the endogenous class I and the exogenous class II pathways is the major determinant in whether the T-cell response will be mediated by CD4⁺ or CD8⁺ T cells (Table I). Antigens arising outside of the cell are preferentially processed by the exogenous pathway and presented by MHC class II molecules (eg, HLA-DR) to CD4⁺ T cells. Examples of exogenous antigens include bacteria and bacterial toxins. Because CD4⁺ T cells provide help for production of antibodies,²⁰ which act outside of the cell, the organization of the system promotes antibody production to extracellular antigens. In addition, CD4⁺ T cells and MHC class II gene products also mediate DTH reactions,²¹ which are directed against exogenous bacteria.

In contrast, antigens arising from the cytoplasm of the cell are presented by MHC class I molecules to α/β TCRs on CD8⁺ T cells. Thus in the case of virus infections, CD8⁺ cells have an important protective role in the immune response, both through cytotoxicity and production of IFN- γ .²² All nucleated cells express MHC class I molecules and are thus potential targets for CD8⁺ T-cell mediated cytotoxicity. Because both viral and tumor-specific proteins are produced in the host cell, and their peptides are processed by the endogenous pathway, CD8⁺ T cells are well suited for surveillance against both viral infections and tumors. Segregation of exogenous and endogenous antigens into their respective pathways is not absolute, however. Extracellular antigen-derived peptides can be presented, under some circumstances, to CD8⁺ T cells,^{23,24} and intracellular antigen-derived peptides can sometimes be presented to CD4⁺ T cells.^{25,26} Such redundancy is typical of the immune system and probably has survival value.

PATTERNS OF CYTOKINE PRODUCTION IN CD8⁺ T-CELL MEDIATED DTH

Cytokine production profiles of CD4⁺ T cells are categorized as T_{H1} or T_{H2} in pattern.²⁷ T_{H1} cells particularly produce IL-2 and IFN- γ , whereas T_{H2} cells preferentially produce IL-4, IL-5, and IL-10. T_{H1} cells are usually responsible for mediating DTH responses, whereas T_{H2} cells, which produce IL-4 and additional helper factors, are responsible for production of IgE and some other antibodies.²⁸ The T_{H1} cytokine IFN- γ is believed to have a key role in DTH and contact sensitivity dermatitis. Functions of IFN- γ include transforming monocytes into macrophages and inducing the endothelial adhesion molecules vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 on endothelium and keratinocytes of involved skin.²⁹ In addition, IFN- γ induces keratinocyte production of the chemokine IFN-inducible protein-10, which is responsible for attracting an infiltrate of leukocytes. Both urushiol-specific (poison ivy) CD8⁺ T cells and nickel-specific CD4⁺ and CD8⁺ human T cells appear to mediate these respective contact sensitivity responses and produce IFN- γ , indicating that whether mediated by CD4⁺ or CD8⁺ T cells, a T_{H1} cytokine pattern with IFN- γ production is prominent.^{30,31}

In general, CD8⁺ T cells that mediate DTH produce cytokine profiles similar to those of CD4⁺ T cells and have been designated T_{Cl} for this T_{H1}-like cytokine profile or T_{C2} for a T_{H2} cytokine profile, which also can occur.^{32,33} The remainder of this review will document this newly recognized ability of T_{Cl} CD8⁺ T cells to act as effector cells for a variety of DTH reactions and allergic contact dermatitis.

CD8⁺ T CELLS IN ACD

The sentinel observation of the newly emerging research into CD8⁺ T cell-mediated DTH is the finding that CD8⁺ T cells often can mediate ACD. The human T-cell response to urushiol (poison ivy), which is a very common form of contact dermatitis in North America, is due predominantly to CD8⁺ T cells.³⁴ Similarly important has been the analogous finding that the murine response to dinitrochlorobenzene (DNCB), a commonly used model of ACD, is due to CD8⁺ T-cell production of IFN- γ . Interestingly, the CD4⁺ T cells also participate in ACD, but they do so by producing downregulatory T_{H2} cytokines that inhibit the local T_{H1} CD8⁺ response and dampen the ACD.³⁵ Likewise, the murine response to the related contact sensitizer dinitrofluorobenzene (DNFB) is dependent on CD8⁺ T cells, with CD4⁺ T cells again having a suppressive role.³⁶ In contrast, the contact sensitizer trinitrochlorobenzene (TNCB, picryl chloride) induces ACD mediated in part by MHC class II-restricted T cells because TNCB is overtly reactive with extracellular proteins and peptides and does not require intracellular activation. However, in MHC class II-deficient mice, it is CD8⁺ effector T cells that mediate ACD to TNCB.³⁶ The response of mice to contact sensitization with the hapten picryl chloride³⁷ and to 4-hydroxyl-3-nitrophenyl acetyl³⁸

also are linked to MHC class I genes, suggesting that these haptens can also be presented to CD8⁺ T cells by MHC class I molecules. Possible mediation of ACD by CD8⁺ effector T cells may explain the occurrence of clinical ACD to urushiol (poison ivy) and to DNCB by HIV⁺ patients who have low CD4⁺ T cell counts.³⁹

Contact allergens generally are small molecules that must react with proteins to be recognized by the immune response. Haptens bind to peptides for presentation to T cells by MHC molecules. Common contact allergens are either chemically reactive haptens or prohaptens capable of being transformed into a chemically reactive intermediate.⁴⁰ The contact sensitizers nickel and cobalt are chelated by the amino acid histidine in proteins to form complexes.⁴¹ DNCB and DNFB are chemically reactive small molecules capable of covalently binding protein by combining with the terminal amino group of lysine residues in proteins.⁴⁰ On the other hand, urushiol, the immunogen of poison ivy, is a prohaptens composed of catechol with a 15 carbon chain lipophilic tail, which may aid in intracellular uptake.⁴² Urushiol is oxidized to a quinone intermediate, which is capable of covalently binding to proteins by nucleophilic substitution.⁴³ This oxidation may occur either extracellularly or intracellularly. In addition, oxidation of urushiol may generate protein-reactive free-radical intermediates.⁴⁴ Hapten protein conjugates may require processing for recognition by T cells.⁴⁵

There is a correlation between the chemical properties of a contact allergen and the pathway of antigen processing, which partially determines the role of CD4⁺ versus CD8⁺ T cells. Thus small lipid soluble hapten molecules (eg, urushiol and DNFB) are capable of entering the cytoplasm and entering the endogenous pathway, leading to sensitization and then reactivity by CD8⁺ T cells. Urushiol also can be processed by the exogenous pathway for presentation to CD4⁺ T cells, presumably by conjugation of urushiol to extracellular proteins, which are later internalized. However, in humans the endogenous pathway for presentation to CD8⁺ T cells is predominant.⁴⁶ This explains why this very common form of ACD is mediated predominantly by CD8⁺ T cells.

Polar-reactive haptens (eg, nickel and cobalt) are predominantly presented by the exogenous pathway to CD4⁺ T cells that mediate ACD.^{47,48} However, 2 recent reports contradict this sizable literature with the finding that nickel-specific CD8⁺ T cells with a T_{H1} cytokine profile are present in the peripheral blood of patients with active ACD.⁴⁹ In contrast, nickel-specific CD4⁺ cells with a T_{H2} profile are found in both patients with active disease and patients with a recent history of ACD.⁵⁰ It was postulated that even nickel dermatitis may be mediated by CD8⁺ T cells.

Haptens that are both lipid soluble and chemically reactive (eg, DNFB) react with both endogenous and exogenous proteins for processing by both pathways and presentation to both CD4⁺ and CD8⁺ T cells. In an interesting contrast with the same mouse strain, DTH foot pad swelling responses to sheep red blood cells, an exogenous particulate antigen, are mediated by CD4⁺ T cells,

whereas ACD to DNFB and to oxazolone are mediated by CD8⁺ T cells.⁵¹ Thus differences in antigen processing control the relative roles of CD4⁺ and CD8⁺ T cells and explain the reported differences between ACD and classic T cell-mediated DTH.

ANTIGEN PROCESSING DETERMINES DTH RESPONSES AND IMMUNE RESISTANCE TO PATHOGENS

Pathogenic infectious agents vary greatly in their molecular interactions with the immune system. Most bacteria are extracellular single-cell parasites, which are internalized by host cells into cytoplasmic endosomes and then processed by the exogenous pathway for presentation to CD4⁺ T cells. Thus classical DTH, such as the tuberculin reaction to *Mycobacteria tuberculosis* proteins and associated cell-mediated immune resistance to extracellular bacteria are mediated by CD4⁺ T-cell mechanisms that largely involve production of IFN- γ .⁵² However, intracellular bacteria, such as *Listeria* and *Mycobacteria* spp, have the additional potential of activating CD8⁺ T cells as antigens enter the intracellular endogenous processing and presenting pathway. Thus CD8⁺ T cells can mediate DTH to *Listeria* and *Mycobacteria* spp and contribute to immune resistance to these organisms.^{53,54}

Viruses are obligate intracellular parasites that use the host protein synthesis machinery. Thus viral antigens are present in the cytoplasm of infected cells and are processed by the endogenous pathway for presentation to CD8⁺ cells. Therefore CD8⁺ T cells have an important protective role in the immune responses to viral infections, both through mediating specific cytotoxicity to virally infected cells^{55,56} and DTH responses. Because all nucleated cells express MHC class I molecules, CD8⁺ cells are able to detect and kill virally infected cells. Obviously, extracellular viral antigens are also released, resulting in a complementary CD4⁺ response.^{57,58} Thus both CD4⁺ and CD8⁺ T cells can mediate DTH and IFN- γ antiviral effects. However, CD8⁺ T cell-mediated DTH offers the potential to kill local cells of any type that are expressing MHC class I molecules in a complex with viral or tumor antigen peptides.

CD8⁺ T CELL-MEDIATED DTH IN ALLERGIC DRUG ERUPTIONS

There is evidence for CD8⁺ T-cell involvement in morbilliform and bullous drug eruptions that may represent a CD8⁺ DTH response in the skin. The histology of drug-induced erythema multiforme⁵⁹ is very similar to graft-versus-host disease, which is known to be mediated by alloimmune MHC-reacting T cells.⁶⁰ In both graft-versus-host disease and erythema multiforme, the infiltrating cells of the epidermis are predominantly CD8⁺ T cells.⁶¹ This contrasts with the dominant CD4⁺ T-cell infiltrate found deeper in the dermis in both conditions, which could possibly represent downregulatory cells analogous to findings in CD8⁺ T cell-mediated murine ACD.

Certain drugs are capable of metabolic transformation into chemically reactive haptens by the cytochrome P450 system.⁶² Keratinocytes contain P450 enzymes,⁶³ which may have relevance to the localization of drug reactions to the skin. Sulfonamides are metabolized to reactive aryl-hydroxide intermediates,⁶⁴ and phenytoin is metabolized to a reactive epoxide intermediate.⁶⁵ Human macrophage myeloperoxidase is also capable of oxidizing sulfonamides to the hydroxylamine.⁶⁶ These reactive intermediates are detoxified enzymatically, and susceptibility to phenytoin has been found to correlate with genetic differences in detoxification of the intermediate.⁶⁷ Metabolic activation of drugs suggests that drugs may act as intracellular haptens and be processed by the endogenous pathway for presentation to CD8+ cells.

An alternative antigen presentation mechanism has been proposed for T-cell responses in drug allergies. Drug-specific T-cell clones were isolated from the blood and skin lesions of patients with drug eruptions to sulfamethoxazole, various penicillins, and lidocaine.⁶⁸ These drugs, although inert, were found to bind directly to existing peptide/MHC class I or class II complexes on glutaraldehyde-fixed APCs, which were able to present drugs to specific CD4+ and CD8+ T-cell clones.⁶⁹ The drug peptide/MHC complex was labile and could be washed away, indicating noncovalent binding. These findings suggest T-cell recognition of the drug, which is bound noncovalently to host peptide/MHC molecules, in the absence of metabolism or processing.⁷⁰

CD8+ T cells reactive with sulfonamide⁷¹ and penicillin^{72,73} have been isolated and cloned from bullous eruptions to these drugs. Penicillin-specific CD4+ T cells have also been isolated but may have more relevance to IgE-mediated reactions.⁷⁴ Although sulfonamide-reactive T cells are present in low frequency in the peripheral blood of patients with morbilliform eruptions to sulfonamides, the fact that very few T cells, in fact as few as one T cell, are needed to elicit a DTH response, suggests that these low numbers may suffice. Perforin, a potent secreted mediator of cytotoxicity, has been identified in the T cells and in the lesions, suggesting that the bullous responses may be mediated by CD8+ class I-restricted, perforin-producing, cytotoxic DTH effector T cells. The involvement of CD8+ T cells in drug reactions may explain the high incidence of cutaneous eruptions to sulfonamide-related drugs seen in HIV+ patients, despite the deficient number and function of CD4+ T cells.⁷⁵

CD8+ T CELLS IN ALLERGIC ASTHMA

Allergen-reactive T cells, acting in part by means of T_{H2} cytokines such as IL-4 and IL-5, are crucial helper T cells for production of IgE antibody in allergic asthma. There now is good evidence that T cells in the asthmatic airway tissues are activated (express CD25), transcribe mRNA, and express cytoplasmic T_{H2} cytokines, such as IL-4 and IL-5. These T_{H2} cytokines, particularly IL-5, along with the chemokine eotaxin released by resident tissue endothelial and epithelial cells, likely participate in recruitment of

eosinophils that release toxic granule proteins (eg, major basic protein and eosinophilic cationic protein) that damage airways and cause the bronchial hyperreactivity that characterizes asthma.

Because most allergens are soluble exogenous proteins, they should be preferentially processed by the exogenous pathway. Therefore it would be expected that the T-cell response to allergens would be predominantly mediated by CD4+ T cells. This indeed is true of the T-cell response to common allergens, such as house dust mites⁷⁶ and pollens.⁷⁷ However, there is additional evidence that CD8+ T cells also may have an important role in the pathogenesis of asthma. First, although most activated T cells in asthma that produce T_{H2} cytokines are CD4+, a significant percentage of the T_{H2} cytokine-transcribing T cells have been shown to be CD8+ T cells in 3 recent studies.⁷⁸⁻⁸⁰ Bronchoalveolar lavage T cells demonstrate selective increases of T-cell receptor V-gene families. These increases are more notable among CD8+ than CD4+ T cells.⁸¹

Local recruitment and then activation of T cells in asthma may be quite analogous to mechanisms of recruitment of T_{H1} cells in conventional cutaneous DTH. Asthma may be a predominant T_{H2} DTH that results from allergen-specific T cells that recruit and activate a local infiltrate dominated by eosinophils. Accordingly, a significant component of this T_{H2} DTH in asthma may be mediated by CD8+ allergen-specific T cells, which produce T_{H2} cytokines.

A particularly striking example that fits with this new idea of CD8+ T_{C2} DTH in asthma occurs in airway inflammatory responses of some individuals that respond to particular chemical respiratory allergen exposure in the work place. In particular, a hapten-dependent asthmatic response that can be quite severe develops in some persons exposed to toluene diisocyanate in auto painting shops or to analogous chemicals in other industries.⁸² It is possible to isolate CD8+ T-cell clones from their airways, suggesting that these haptens can be processed by the intracellular (endogenous) pathway for presentation by class I MHC molecules to CD8+ cells.⁸³ This is directly analogous to the processing of some lipid-soluble allergic contact haptens (eg, urushiol and DNCB).

The association of viral infections with asthma provides additional support for a role of CD8+ T cells in allergic asthma.⁸⁴ Viral-specific CD8+ cytotoxic T cells grown in the presence of IL-4 can be switched to a T_{H2} cytokine profile (called T_{C2}), with production of IL-5.⁸⁵ Challenge of the airways with viral peptide then induces an eosinophilic infiltration.⁸⁶ This may help to explain both the link between viral infections and asthma, as well as the difficulty atopic patients have in clearing viral respiratory infections.

The above findings suggest CD8+ cells may have relevance to intrinsic asthma, which currently is regarded as an idiopathic disease, in which exogenous allergens have not been shown causative. It is postulated that haptens derived from environmental agents, such as cigarette smoke, could have access to the class I pathway either by intracellular metabolic activation or direct binding to

peptides in MHC class molecules. The resulting CD8+ DTH response could lead to airway hyperreactivity. If CD8+ DTH effector T cells play a role in asthma, then current efforts to find allergen peptides for desensitization of asthma by class II associations will have to be extended to allergen peptides that interact with class I MHC molecules. Also, if DTH mechanisms play a role in intrinsic asthma, efforts should extend beyond allergens that induce IgE wheal and flare cutaneous responses to an examination of potential allergens that may induce DTH mechanisms.

CD8+ T CELL-MEDIATED DTH IN AUTOIMMUNE DISEASES

On the basis of antigen-processing considerations, endogenous cytoplasmic antigens should be preferentially presented by MHC class I molecules for a CD8+ T-cell response. Accordingly, there must be protective mechanisms against such autoimmunity. In failures of tolerance, CD8+ T cells should therefore have an important role in ensuing autoimmune responses. Diseases that are associated with MHC class I molecules, such as Reiter's syndrome⁸⁷ and Behcet's Disease,⁸⁸ may be mediated by a CD8+ DTH effector T-cell response to cytoplasmic antigens presented by the endogenous pathway. In fact, many autoimmune diseases are associated with particular MHC class I molecules, such as B27 in ankylosing spondylitis⁸⁹ and psoriatic arthritis,⁹⁰ or MHC class II molecules, such as DR3 and DR4 in autoimmune juvenile diabetes⁹¹ and rheumatoid arthritis.⁹² These MHC associations can be linked to specific amino acid residues in the peptide-binding groove of the MHC molecule that should bind the relevant self peptides.⁹³ It is postulated that association of an autoimmune disease with an MHC allele reflects presentation of specific autoantigen peptides by that MHC molecule.

Both CD4+ and CD8+ T cells infiltrate the pancreatic islets of NOD mice with experimental diabetes, and accelerated diabetes in these mice is transferable with either CD4+ or CD8+ T cells.^{94,95} Infiltrating CD4+ and CD8+ cells both produce IFN- γ , suggesting a T_{H1} cytokine pattern of classic DTH.⁹⁶ Thus it seems likely that both CD4+ and CD8+ DTH effector T cells may play a role in experimental diabetes and that CD8+ DTH effectors may have additional pathogenic properties by means of their specific cytotoxic function for MHC class I-restricted antigens.

CD8+ T cells also may have a role in human autoimmune diabetes. Patients with newly diagnosed insulin-dependent diabetes have an increased proportion of activated CD8+ T cells in the peripheral blood,⁹⁷ and in a prospective twin study, elevated levels of circulating activated CD8+ T cells were strongly predictive of the development of diabetes.⁹⁸

Experimental autoimmune thyroiditis also involves an interaction between CD4+ and CD8+ T cells. This condition can be induced by immunization with mouse thyroglobulin and can be transferred by T cells.⁹⁹ Both CD4+ and CD8+ T-cell clones, producing T_{C1} cytokines, have

been derived from lesions of experimental autoimmune thyroiditis.¹⁰⁰

CONCLUSIONS

CD8+ T cells mediate DTH reactions and play a major role in ACD, drug eruptions, and the response to viral pathogens. Furthermore, CD8+ cells may mediate chemical inhalant allergies, as well as certain autoimmune diseases. The role of CD8+ cells in inflammation extends to conditions that are initiated by CD4+ T cells, such as asthma, and autoimmune conditions, such as Type 1 insulin-dependent diabetes. Thus CD8+ T cells must be regarded as effectors of DTH and immunopathology, with a role exceeding that of "suppressor/cytotoxic" T cells.

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