

CME

Immunologic Principles of Allergic Disease

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JDDG; 2007 · 5:1015–1028

Submitted: 8. 6. 2007 | Accepted: 27. 7. 2007

Section Editor
Prof. Dr. Jan C. Simon,
Leipzig

Keywords

- allergology
- Immunology
- B-cells
- antigen presenting cells
- antibody

Summary

Allergy either results from a pathological excessive immune reaction, or from the defective induction of tolerance to otherwise harmless antigens. Allergic reactions are mounted by mechanisms of innate and adaptive immunity. The development of an allergic response can be divided in sensitization and elicitation phases. Immediate type allergic reactions (e.g. anaphylaxis, urticaria, rhinoconjunctivitis allergica, allergic asthma) are mediated by IgE antibodies which are produced by B cells stimulated by allergen-specific Th2 cells. Crosslinking of allergen-specific IgE on membrane surfaces of mast cells and basophilic granulocytes leads to release of soluble mediators which may cause systemic symptoms within minutes to hours. The following infiltration of eosinophilic granulocytes and Th2 cells directs chronic inflammation.

Humoral cytotoxic immune reactions (e.g. drug induced cytopenia) are mediated by IgG and IgM antibodies which are directed against membrane associated antigens. IgG and IgM antibodies directed against soluble antigens elicit immune complex mediated cytotoxicity (e.g. drug induced vasculitis). Delayed type immune reactions (e.g. contact dermatitis) are based on the activation of antigen specific CD4⁺ and CD8⁺ T cells and need 24 h to 48 h to develop. Upon recurrent contact with identical antigens, recruitment of CD4⁺ and CD8⁺ T cells cause inflammation and cytotoxic induced apoptosis in target cells as well as cytokine mediated leukocyte infiltration. Subsequent immigration of CD4⁺ Th2 cells provides anti-inflammatory mechanisms leading to resolution of the inflammatory response and tissue repair.

Basic Structures and Concepts of the Immune System

An allergy is a disorder produced when the immune system responds to otherwise harmless antigens. Coombs and Gell have divided hypersensitivity into four main types for didactic purposes, although in clinical practice distinguishing these is difficult and there may be humoral and cellular immune responses may overlap or occur simultaneously (Table 1).

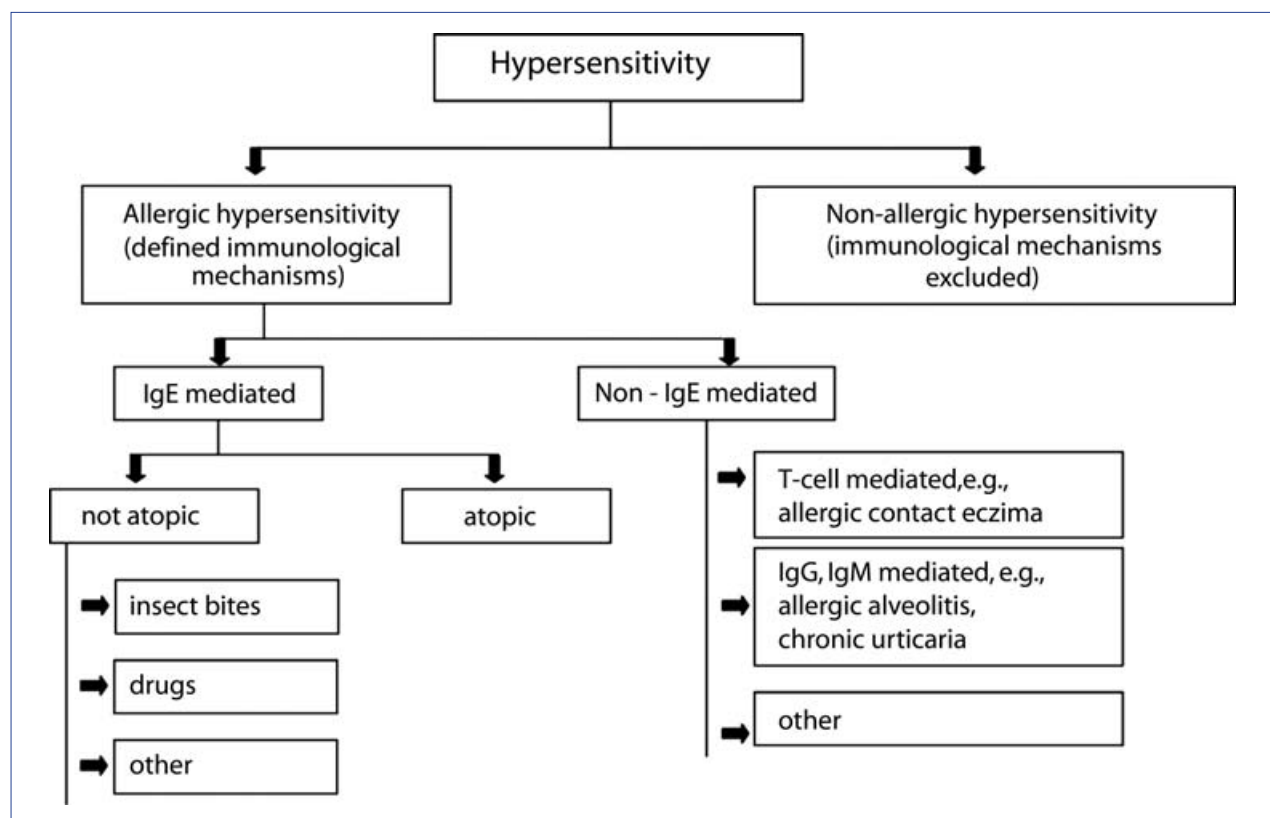
For clinical classification of hypersensitivity, a further nomenclature was recently proposed (Figure 1) which distinguishes between allergic and nonallergic hypersensitivity and also between IgE-mediated and non-IgE-mediated. This classification is aimed in particular at drawing a clear boundary with non-immunological adverse reactions (known as “pseudoallergies” or intolerance).

Allergic reactions, like any immune response, are mainly mediated by leukocytes which develop from pluripotential stem cells in the bone marrow and are responsible for innate (nonspecific) and acquired (specific) immunity. **Innate immunity** is mediated

Innate immunity is mediated by various humoral (e.g., alternative complement activation, anti-microbial peptides) and cellular defense mechanisms (e.g., macrophages).

Table 1: Classification of immune responses by Coombs and Gell.

Antibody-mediated hypersensitization			Cell-mediated hypersensitization
Type I	Type II	Type III	Type IV
Immediate hypersensitization IgE-mediated	Humoral cytotoxic immune response	Immune complex-mediated immune response	Delayed hypersensitization T cell-mediated
- Allergic rhinitis - Bronchial asthma	- Drug-induced cytopenia	- Immune complex-vasculitis - Exogenous allergic alveolitis	- Contact allergy - Drug-induced exanthema

**Figure 1:** Clinical classification of hypersensitivity, modified after SG Johansson et al. 2001.

Innate immunity is nonspecific and does not change when the same pathogen is encountered again.

Acquired immunity is mediated by antigen-specific humoral (e.g., antibodies) and cellular components (e.g., lymphocytes).

Acquired immunity leads to the development of immunological memory.

The cells of the innate immune system can recognize and ward off common characteristics of pathogens, or PAMPs (pathogen-associated molecular patterns), via invariant receptors.

by various humoral (e.g., alternative complement activation, anti-microbial peptides) and cellular defense mechanisms (e.g., macrophages) and is especially active in the early phase of the body's defense against a pathogen. It is nonspecific and does not change when the same pathogen is encountered again. **Acquired immunity** is mediated by antigen-specific humoral (e.g., antibodies) and cellular components (e.g., lymphocytes). It also leads to development of immunological memory.

The cells of the innate immune system can recognize and ward off common characteristics of pathogens, or **PAMPs (pathogen-associated molecular patterns)**, via invariant receptors, but without developing a memory to provide protection against renewed threat by the same pathogen. Stimulators of innate immunity, which are not synthesized by the human body, include lipopolysaccharides, peptidoglycan, and non-methylated CpG islands in bacterial DNA. PAMPs are recognized by various **pattern recognition receptors (PRR)**, e.g., Toll-like receptors, type-II lectin receptors, C-type lectin-receptors, Nod proteins, and integrins.

The cell types belonging to the innate immune system include macrophages, neutrophils, basophils, and eosinophilic granulocytes, natural killer cells, and dendritic cells. PRRs are also expressed by resident tissue cells such as keratinocytes, fibroblasts, and endothelial cells, which produce inducible nitric oxide synthase (iNOS) and antimicrobial peptides after stimulation. Macrophages and mast cells undergo final differentiation in tissue where they initiate inflammation, for instance via macrophage phagocytosis of bacteria and cell debris and recruitment of other inflammatory cells. Macrophages have a high level of phagocytotic activity. Complement C3b, which binds to the pathogen surface, can facilitate phagocytosis via complement receptors. Facilitation of phagocytosis by C3b is known as opsonization. C3 is a central component of the complement system and is constitutively formed by resident tissue cells such as keratinocytes. The **complement system** is involved as a humoral component in innate and acquired immunity. It consists of plasma proteins (designated by the letter C followed by a number) and is a complex enzyme system. The enzyme complexes and breakdown products arising upon activation ultimately lead to increased phagocytosis, histamine release, and cytolysis. Granulocytes, which circulate in large numbers in the blood, are recruited to sites of inflammation as effector cells. After endothelial adhesion and trans endothelial migration via chemokine gradients, they contribute significantly by phagocytosis to eliminating harmful pathogens.

Secretory **mast cells** contain special cytoplasmic granules that can be released very quickly after activation (see below). Mast cells play a role in the defense against parasites and recruitment of other secretory inflammatory cells such as basophils and eosinophilic granulocytes (see below).

Antigen-presenting cells (APC) travel as precursor cells from the bloodstream into peripheral tissue where they become specialized as antigen-processing and antigen-presenting cells. Antigen-presenting cells of the skin include macrophages, dermal dendritic cells, and Langerhans cells. Langerhans cells are found in the suprabasal layers of the epidermis; unlike other dendritic cells, they tend to be stationary and can remain in the peripheral tissue for several months. In the skin, antigen acquisition occurs after penetration of the antigen through the stratum corneum of the epidermis. In the lungs and intestine, there is only a single epithelial layer between dendritic cells and antigens, allowing luminal antigens to be directly taken up.

Antigen is processed in intracellular compartments of the antigen-presenting cells where it undergoes proteolysis. Afterward, a representative repertoire of antigen fragments is presented on the cell surface using specialized immune receptors, MHC molecules.

Major histocompatibility complex (MHC) is a region comprised of three genomic complexes on chromosome 6. It regulates synthesis of proteins which mediate antigen presentation to cytotoxic CD8⁺ T cells (**class I MHC**) and CD4⁺ T cells (**class II MHC**). They restrict the interaction of antigen-presenting and T cells in such a way that T cells are only activated if presented with antigens in conjunction with MHC molecules. Class I MHC molecules bind peptide fragments (3–25 amino acids) of proteins that were degraded by 26S proteasome in the cytosol. Dendritic cells in particular have the ability to bind antigens taken up via endocytosis to class I MHC molecules. This process, known as “cross-presentation”, is especially relevant for tumor-associated and viral immune responses in order to avoid endogenous expression of tumor antigen or viral infection of the dendritic cells. While class I MHC is expressed by all nuclear cells, class II MHC is mainly present on antigen-presenting cells. Class II MHC binds antigen fragments which, after endocytosis, are degraded in the acidic endolysosomal compartment. Dendritic cells are thus able to present the proteins they have encountered on the cell surface. Lipids, glycolipids, lipopeptide and other hydrophobic substances are presented to CD1 restricted T cells.

The **CD1 antigen-presenting system** is composed of 5 transmembranous glycoproteins (CD1a-CD1e) and elicits a stronger immune response in the presence of foreign lipids.

For distinguishing “self” and “foreign” by dendritic cells, recognition of PAMPs via TLRs is essential. Along with a high concentration of antigens of the same type, which are found in only a small number of different MHC peptide complexes, but in a high number of cells on the surface of dendritic cells, it is likely that local signals such as cytokine milieu in peripheral tissues contribute to damage. The result is that

The complement system is involved as a humoral component in the innate and acquired immune systems.

MHC mediates the presentation of antigens to cytotoxic CD8⁺ T cells (class I MHC) and CD4⁺ T cells (class II MHC).

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an alarming situation with a tolerogenic immune response is transformed into a more threatening one with a subsequent immunogenic immune response. Dendritic cells are key cells in innate immunity and bridge innate and acquired immune responses. The initiation of acquired immunity occurs in the secondary lymphoid organs, i.e., the spleen and lymph nodes, as well as in mucosa-associated lymphoid tissue (MALT) such as tonsils or the Peyer's plaques in the intestine (Table 2).

B lymphocytes and T lymphocytes mature in the primary lymphoid organs, bone marrow and thymus, and recirculate via the blood into secondary lymphoid organs. They bear antigen-specific receptors which recognize antigen presented by dendritic cells. These specific receptor structures are realized in primary lymphoid organs by random recombination of variable receptor segments and pairwise binding to variable segments. These variable segments include parts of the heavy (V_H) and light chains (V_L) of the **immunoglobulins** and parts of the α - and β -chain of the **T-cell receptor** (Figure 2).

This allows identification of nearly all antigens. The acquired immune system is activated, for example, when the innate immune system is not able to defend the body against a new infection. A recirculating lymphocyte is presented in peripheral lymphoid tissue with antigen which stimulates proliferation. The proliferating lymphocytes differentiate into effector cells which can eliminate infection. They also differentiate into **"memory" cells**, which when they re-encounter the same pathogen, respond with a targeted defense (immunological memory). Among memory T cells (T_M) a distinction is made between central memory cells (T_{CM}), which express CCR7 and migrate into lymphatic tissue, and effector memory cells (T_{EM}), which do not express CCR7 and migrate into inflamed tissue. In normal skin, T cells are found around postcapillary venules in about the same proportion of CD4- to CD8-positive cells with a "memory" phenotype (CD45 RO⁺). The epidermis contains only 2-3 % of all of the T cells of the skin.

An understanding of the acquired immune system is important to understanding allergies. Lymphocytes have various recognition systems for intra- and extracellular antigens. **B lymphocytes** recognize antigens via cell-bound immunoglobulins and upon activation secrete immunoglobulins as soluble antibodies. Immunoglobulins/antibodies are glycoproteins which are divided into 5 classes based on amino acid sequence, molecular weight, and carbohydrate content: IgG, IgM, IgA, IgD and IgE.

The common basic structure of all immunoglobulins consists of two identical heavy and light chains which are connected by disulfide bridges. Papain treatment results in two antigen-binding fragments: a Fab fragment and an Fc fragment, which does not bind antigen (Figure 3). Immunoglobulin switching involves altered production of immunoglobulin class (IgG, IgA, IgE and IgM) while maintaining antigen specificity. It requires the presence of T cells and their cytokines. IFN- γ leads to a change to IgG1 and IgG3; IL-4 and IL-13 lead to a change to IgE and IgG4; and TGF- β and IL-5 lead to a change to IgA.

Table 2: Overview of local components of the immune system. MALT (mucosa-associated lymphatic tissue), GALT (gut-associated lymphatic tissue), BALT (bronchial-associated lymphatic tissue).

Primary lymphoid organs	Secondary lymphoid organs	Peripheral tissue
- Bone marrow - o B cell maturation - Thymus - o T cell maturation	- Lymph nodes - Spleen - MALT - o GALT: Peyer's plaques, tonsils, appendix - o BALT	- Blood vessels - Heart - Skin - Lung - Intestine
Antigen-independent, genetically determined	Antigen-dependent clonal expansion and differentiation	Modulation and regulation via microenvironment

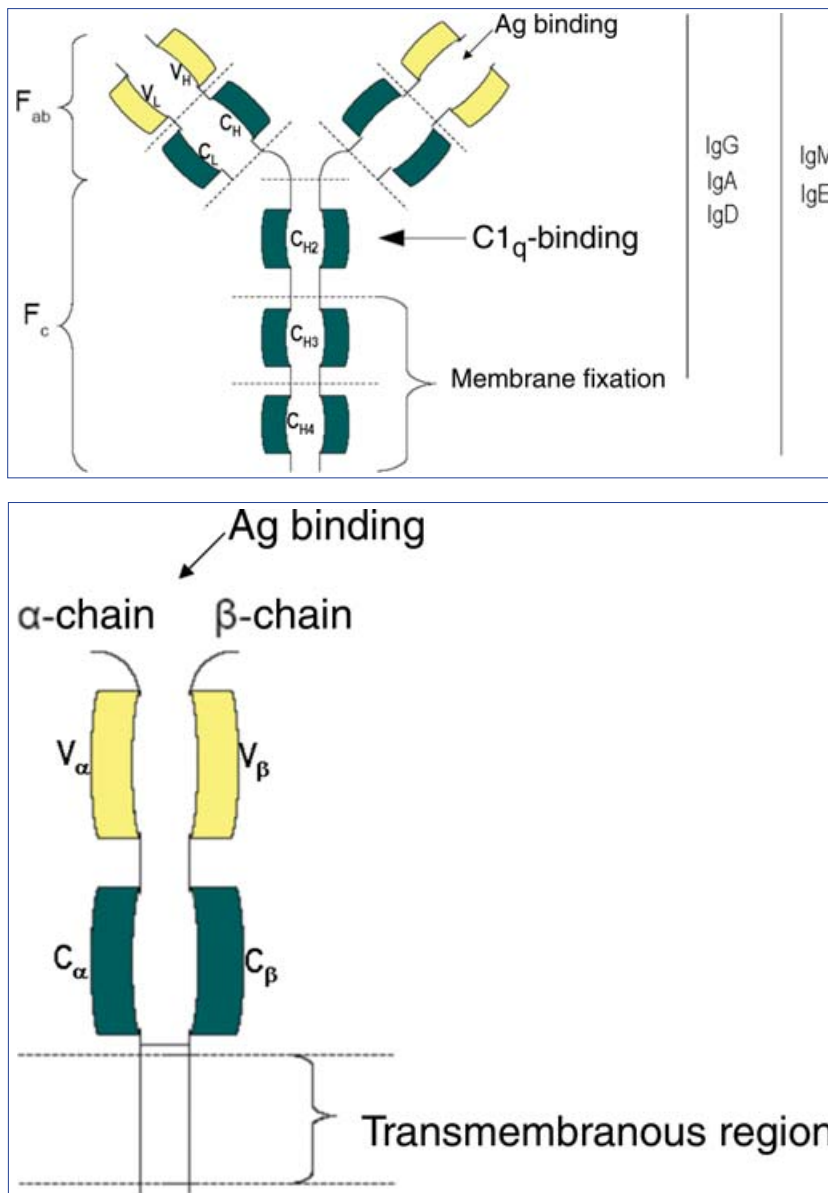


Figure 2: Immunoglobulin structure: V_L = variable light chain, V_H = variable heavy chain, C_L = constant light chain, C_H = constant heavy chain, C_{H2-4} = constant heavy chain domains.

Structure of the T-cell receptor: V_α = variable α-chain, V_β = variable β-chain, C_α = constant α-chain, C_β = constant β-chain.

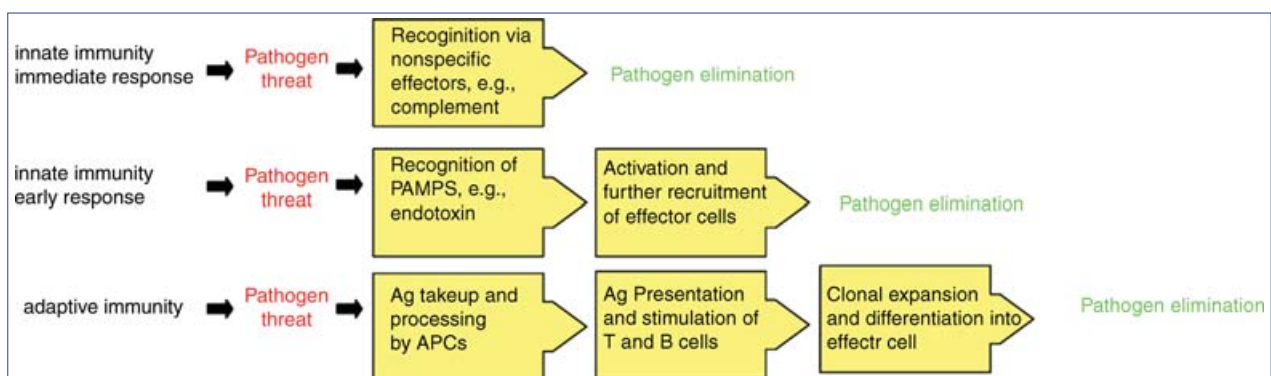


Figure 3: Overview of innate and adaptive immunity modified after CA Janeway et al. 2004. PAMP (pathogen-associated molecular patterns), APC (antigen-presenting cells), Ag (antigen).

While CD8⁺ cytotoxic T cells eliminate target cells, CD4⁺ helper T cells activate B cells and macrophages.

T lymphocytes only recognize antigens in connection with MHC on the cell surface of antigen-presenting cells.

Naive CD8⁺ T cells interact with class I MHC and differentiate into cytotoxic CD8⁺ T cells (T_c) by co-stimulatory signals from antigen-presenting cells or by prior activation of antigen-presenting cells by CD4⁺ helper T cells. They may be divided based on secreted cytokines into T_c-1 (IFN- γ) and T_c-2 (IL-4, IL-5) cells. CD4⁺ T cells interact with class II MHC on the surface of antigen-presenting cells. The differentiation of naive CD4⁺ Th₀ (helper) cells (CD45-RA⁺, CD45RO⁻) is determined by interaction with surface molecules and especially cytokines of antigen-presenting cells. CD4⁺ Th cells are divided into Th1 and Th2-subpopulations based on secreted cytokine profile. IL-12 leads to **Th1 differentiation** which leads to activation of macrophages and induction of opsonizing antibodies (IgG) and ultimately cell-mediated immunity. It is characterized by production of IFN- γ . IL-4 and IL-6 lead to **Th2 differentiation** which can stimulate proliferation and differentiation of B cells and influence antibody isotypes produced by B cells (see above) and ultimately leads to humoral mediated immunity. It is characterized by production of IL-4 and IL-5. TGF- β leads to differentiation of Th3 cells, which can suppress Th1 and Th2 T cells. They are characterized by production of IL-10 and TGF- γ . IL-10 and IFN- γ lead to differentiation of a subgroup of CD4⁺ T cells, the CD25-expressing **regulatory T cells** (T_{reg}). T_{reg} may be divided into natural (generated in the thymus) and acquired (induced in peripheral tissue) T_{reg}. While the effects of the former are mainly dependent on contact, the latter inhibit Th1 and Th2 cells by producing IL-10 and TGF- γ . A further subgroup consists of regulatory T1 cells (Tr1), which also mediate their suppressive effects via production of IL-10. T_{reg} can regulate allergic and non-allergic immune responses. The extent of regulation determines the immune response. In addition to suppressing Th1 and Th2 cells, other presumed effects include inhibition of antigen-presenting cells and mast cells, a regulatory function on B cells with suppression of allergen-specific IgE and induction of IgG4 and IgA. Allergen-specific IgG4 is also induced during specific immunotherapy and is supposed to prevent IgE-mediated de-granulation by effector cells.

Along with the “classic” cells of the immune system, signals from aggregations of tissue cells where an immune response is initiated or occurs, are increasingly important in local modulation of the immune response. For instance, keratinocytes are one of the main sources of proinflammatory (IL-1 α , - β , TNF- α , IL-6) and immunomodulatory cytokines (IL-7, IL-12, IL-15, IL-18) of the skin which are secreted in response to nonspecific stimulation, e.g., by trauma, infection, or UV light. Regulation of expression of surface molecules enables keratinocytes (MHC-II, ICAM-1, CD40, BB-1) to come into contact with lymphocytes. Endothelial cells lining the vessels play a decisive role in recruitment and targeted tissue-specific invasion (“homing”) of leukocytes. Like keratinocytes, fibroblasts also synthesize cytokines and can come into direct contact with immune cells via surface molecules. The recruitment of leukocytes in the skin, for instance, occurs in three phases: “attachment and rolling”, adhesion, and transmigration/extravasation. The attachment and rolling of leukocytes is initiated via binding of glycoproteins (Sialyl Lewis^x groups) to selectin (CD62P and CD62E) on endothelial cells. Additionally, rolling is mediated by α 4 β 1-integrins by interaction with endothelial VCAM-1, especially in the absence of selectin. Chemokines, which are bound to apical proteoglycans on the endothelial cells, ensure clustering of α 4-integrins. The chemokines CCL27 and CCL17 and the expression of cutaneous, lymphocyte-associated antigen (CLA) on the T-cell surface appear especially important for T cell homing in the skin. The transient rolling of leukocytes on the endothelial surface ultimately leads to stronger binding due to interaction of leukocytic LFA-1 (CD11a) or Mac-1 (CD11b) with ICAM-1 (CD54). Transmigration (extravasation, diapedesis) refers to the crossing of interendothelial junction sites and basement membrane in order to penetrate the tissue. This process also requires the shearing forces of blood flow. In addition, various integrins (α 1 β 1, α 2 β 1, α 5 β 1 integrins) and CD44 on leukocytes are presumably responsible for binding on components of the extracellular matrix (collagen, fibronectin, hyaluronic acid) enabling further migration.

An allergic response consists of a sensitization and an effector phase.

The development of an allergic reaction is divided for didactic purposes into two phases, the sensitization phase and the effector phase, although they always occur simultaneously.

Immediate hypersensitivity (type I) reactions such as anaphylaxis, acute urticaria, allergic rhinoconjunctivitis, and bronchial asthma

In the strict sense of the term, anaphylaxis refers to an IgE-mediated, generalized allergic reaction. In type I responses signals are generated during the sensitization phase that cause differentiation of naive $CD4^+$ Th₀ cells into Th2 cells. Next, cytokines secreted by Th2 cells and co-stimulatory surface signals lead to stimulation of IgE-producing B cells. IgE binds via Fc fragment to high-affinity $Fc\epsilon RI$ on mast cells and basophils so that upon renewed contact (effector phase) the antigen is bound to cellular IgE and $Fc\epsilon RI$ cross-linking can occur. This leads to activation of mast cells and basophils and thus release of preformed as well as newly formed mediators that can produce local and/or systemic symptoms such as allergic rhinoconjunctivitis, urticaria, and bronchial asthma within minutes or hours (Figure 4)

Many allergens that trigger a type I reaction are low-molecular weight, highly water-soluble proteins that enter the body via the mucosa of the respiratory and digestive tracts. Even the tiniest amounts are sufficient to cause an IgE-mediated reaction in sensitized persons. The recognition of antigens in class II MHC molecules and especially cytokines secreted by antigen-presenting cells leads to Th2 differentiation of $CD4^+$ T cells. This occurs early on in the development of an immune response and plays a decisive role in the adaptive immune response. The cytokines IL-4 and IL-6 play a key role in Th2 differentiation of naive $CD4^+$ T cells, which is important in the development of a type I reaction.

Th2 cells upregulate the surface molecule CD40 ligand, with which they stimulate the CD40 molecule on B cells. Along with the influence of secreted IL-4, IL-5 and

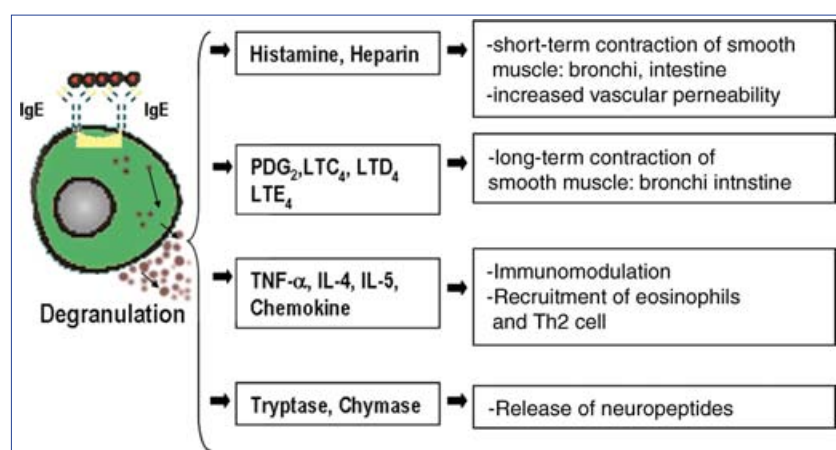
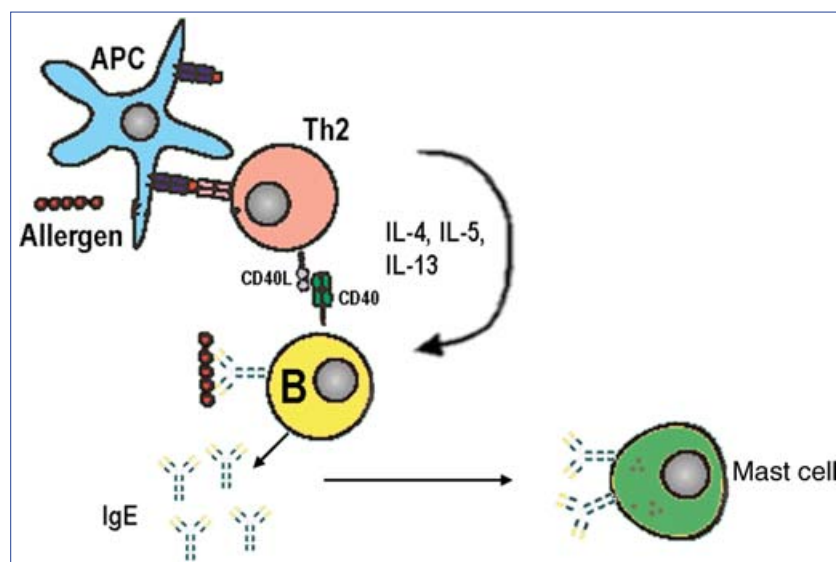


Figure 4: Development of a type I allergy. APC (antigen-presenting cell).

The effector phase of a type I reaction may be divided into an early reaction, which begins within seconds or minutes, and a delayed reaction, which occurs after 8–12 hours.

Mast cells are the most vital effector cells in early type I allergic reactions. Their activation leads to release of preformed granules (especially histamine and heparin) as well as formation of leukotrienes and cytokines.

Type II hypersensitivity is mediated by IgG or IgM antibodies that target membrane-associated antigens.

IL-13 in allergen-specific B cells, there is also class switching of immunoglobulins with production of IgE. The ability to produce increased amounts of IgE is determined by genetic and environmental factors. In industrialized nations, the lack of viral and bacterial infections during childhood (i.e., lacking immune responses that would produce Th1 differentiation) due to improved hygiene, vaccinations, and increased antibiotic use, has led to the much discussed “hygiene hypothesis”, which suggests that the unrestricted production of Th2 cells is responsible for the increase in allergies.

The effector phase of a type I reaction may be divided into an **early response**, beginning within seconds or minutes, and a **delayed response**, occurring after 8–12 hours. This is explained by immediate release of substances such as histamines and proteoglycans, on the one hand, which are already preformed in mast cells, and newly formed substances such as lipids and cytokines (see below), on the other. Mast cells are located along the mucous membranes and in connective tissues. Allergens crosslink allergen-specific IgE's, which are bound to the high-affinity FcεRI on mast cells and basophils. Mast cells and basophils that are thus activated release preformed granules which contain biogenic amines (especially histamines) and proteoglycans (especially heparin). The activation of phospholipase A2 causes the release of membrane lipids followed by development of lipid mediators such as leukotrienes (LTC₄, LTD₄ and LTE₄) and prostaglandins (especially PGD₂). There is also secretion of cytokines, the most important of which are TNF-α, IL-4 and IL-5.

In anaphylactic reactions, histamine is mainly effective via H1 receptors, leading to smooth muscle contractions in the lungs and intestine as well as increased vessel permeability. The effects of histamine are very brief due to rapid breakdown and diffusion.

Heparin and other proteoglycans form a granule matrix and are important for the proper release and availability of secreted histamine, cytokines, and enzymes (tryptase and chymase). Leukotrienes bind to specific receptors and after several hours lead to long-lasting smooth muscle contractions such as seen in asthmatic bronchoconstriction. Mast cell tryptase in patient serum is an important clinical parameter of mast cell activation. Along with stimulation of smooth muscle cells, proteolytic cleavage of neurogenic receptors leads to release of neuropeptides.

With the help of diverse chemokines, the cytokines TNF-α, IL-4 and IL-5 from mast cells play an immunomodulatory role and contribute to formation of the cellular infiltrate following the anaphylactic reaction as a type of delayed reaction. The infiltrate consists primarily of eosinophilic granulocytes and Th2 cells. Activated eosinophilic granulocytes release toxic granules (eosinophilic cationic peptide [ECP], eosinophil-derived neurotoxin [EDN], major basic protein [MBP]) and reactive oxygen species, which lead to tissue damage. Prostaglandins and cytokines, secreted by eosinophilic granulocytes, exacerbate the inflammation and significantly contribute to the development of chronic illness if exposure to the allergen persists, as seen for instance in chronic bronchial asthma with airway remodeling. Eosinophilic granulocyte and Th2 cells are the most vital effector cells in type I delayed hypersensitivity. The activation of eosinophilic granulocytes leads to release of toxic granules and oxygen free radicals that lead to tissue damage and promote the development of chronic inflammation. The re-appearance of symptoms upon re-encountering the allergen, despite avoidance of exposure for a longer period of time, is due to memory cells. Certain memory cells are long-lived, although the factors that make them so are not precisely known.

Humoral cytotoxic immune responses (type II) such as in drug-induced cytopenia or chronic urticaria

After binding of the antibody, the cell is destroyed. Depending on the number of bound antibodies, for example, the cell may be destroyed by complement-mediated cytolysis, antibody-dependent cell-mediated cytotoxicity (ADCC), or phagocytosis. The reaction occurs within minutes. Clinical severity depends strongly on cell type and tissue in which the reaction occurs. This is understandable if one recalls the variety of autoimmune diseases such as bullous pemphigoid, autoimmune hemolytic anemia, and autoimmune-mediated chronic urticaria, which are all triggered by type II reactions. The classic example of a type II response is drug allergy. The accumulation of substances or their metabolites in membrane structures, with subsequent formation

of IgG, can lead to hemolytic anemia and thrombocytopenia. Such drugs include penicillin, cephalosporin, hydrochlorothiazide, and methyldopa. Other drugs, such as sulfonamide and metamizol can cause granulocytopenia.

The binding of IgG or IgM antibodies to membrane-associated antigens allows binding of C1_q in the Fc fragment of the antibody and thus activation of the classic complement pathway. The subsequent binding factors C2 and C4 form C3 convertase, a protease that also arises in the two other activation pathways of the complement system. C3 convertase cleaves C3 into C3b, which initiates further polymerization and cleavage of complement factors in the complex with C3 convertase so that the formation of lytic (C5b-9) complex on the cell surface is initiated and can lead to cytolysis. Along with C3a and C5a important inflammation-mediators – called anaphylatoxins – arise which lead to smooth muscle contractions, increased vessel permeability, and activation of mast cells with release of histamine and TNF- α .

In antibody-dependent cell-mediated cytotoxicity (ADCC), the antibody-coated target cell is destroyed by natural killer (NK) cells. They express Fc γ RIII (CD16), which recognizes IgG1 and IgG3. After binding, the target cell is destroyed by release of perforin/granzyme-containing granules.

Fc γ receptors with a high or low affinity for IgG are carried by many cells such as neutrophils, monocytes. Phagocytosis is triggered after binding. Facilitation of phagocytosis by antibodies is referred to as opsonization. C3b, which is bound to complement receptors, is another opsonin.

Immune complex-mediated immune responses (type III) such as exogenous allergic alveolitis or immune complex-associated vasculitis

Antigen and antibodies form immune complexes in vessels and tissues which can be bound by the Fc γ receptors of mast cells and other leukocytes and lead to their activation. Immune complexes can also activate complement. The reaction occurs within 4-6 hours. There is a predilection for organs such as the lungs and kidneys that have an ample blood supply. Disease activity caused by immune complexes depends on their size, affinity and antibody isotype. Immune complex reactions are seen, for instance, in exogenous allergic alveolitis (birdkeeper's lung, farmer lung) and immune complex-associated vasculitis (drug-induced).

Immune complexes are normally phagocytosed or broken down after they arise, depending on size. On the one hand, immune complexes arising with antigen excess in an insufficient humoral immune response, e.g., in patients with immunosuppression or insufficient antibody production, can persist and collect in vessel walls and tissue, especially in glomeruli, and cause inflammatory reactions such as immune complex-associated vasculitis or glomerulonephritis. On the other hand, repeated allergen exposure can lead to excess IgG antibodies with local hyperimmunity and formation of immune complexes, especially in the skin and lungs. The immune complexes bind via Fc γ receptors to leukocytes, neutrophils, basophils, and mast cells, activating them and causing an inflammatory reaction such as seen in immune complex-associated vasculitis and alveolitis. A less important mechanism occurs with activation of complement C3a and C5a, which contributes to the inflammatory reaction by ligation of complement receptors on leukocytes.

Delayed hypersensitivity (type IV) such as in allergic contact dermatitis or drug-induced exanthema

Type IV immune responses are not mediated by antibodies, but arise from activation of antigen-specific effector T cells that are stimulated during the sensitization phase by antigen-presenting cells. In hapten-induced allergic contact dermatitis, e.g., reactions to chemicals or metals, CD8⁺ cytotoxic T cells are also important effector cells, leading to clinical symptoms with 24-48 hours. Haptens are low molecular weight molecules (e.g., in metals such as nickel or cobalt) that become complete antigens after binding with a local immunogenic carrier molecule. They can also bind directly to MHC-coupled peptides. Haptens are very small and can easily penetrate the epidermal barrier, especially if they also have irritative effects. The development of a contact allergy requires interaction between a hapten and skin cells or proteins.

After contact with a hapten, Langerhans cells travel during the sensitization phase as epidermal antigen-presenting cells through afferent lymph vessels into regional lymph nodes. The cytokines IL-1 β and TNF- α play a key role in this process. Recent studies

Type III hypersensitivity is mediated by IgG and IgM antibodies that target soluble antigens.

Delayed type hypersensitivity is mediated by activation of antigen-specific effector T cells, mainly CD4⁺.

CD8⁺ T cells, which secrete IFN- γ , are generated under the influence of IL-12 via MHC class I-bound antigens, while CD4⁺ T cells are generated via MHC class II-bound antigens as regulatory cells which secrete IL-10.

indicate that Langerhans cells² might not be required for the development of contact sensitization, but that interstitial dermal dendritic cells can take over sensitization. The faster migration of dermal dendritic cells in lymphoid tissue is an important factor. During their migration, dendritic and Langerhans cells mature into antigen-presenting cells and regulate MHC molecules and co-stimulatory molecules on their cell surface up, enabling them to stimulate naïve T cells residing in lymph nodes. CD8⁺T cells, which secrete IFN- γ , are generated under the influence of IL-12 via MHC class I-bound antigens, while CD4⁺T cells are generated via MHC class II-bound antigens as regulatory cells which secrete IL-10. T cells express CLA (cutaneous lymphocyte-associated antigen) as a “homing” marker, proliferate under the influence of IL-2, migrate from the lymph nodes, and are carried by the blood to the skin. Certain T cells downregulate the chemokine receptor CCR7. These belong to the pool of peripheral memory T cells that can migrate to peripheral tissues. Memory cells that express CCR7 recirculate in the bloodstream and can migrate again to the lymph nodes (Figure 5). The sensitization phase lasts 10–15 days and is usually asymptomatic.

After renewed contact between the skin and the same antigen, the antigen is taken up as in the sensitization phase by antigen-presenting cells that quickly migrate into regional lymphoid tissue and present antigen to sensitized memory T cells. Cytokines such as IL-1 β and TNF- β as well as chemokines are released by activated keratinocytes,

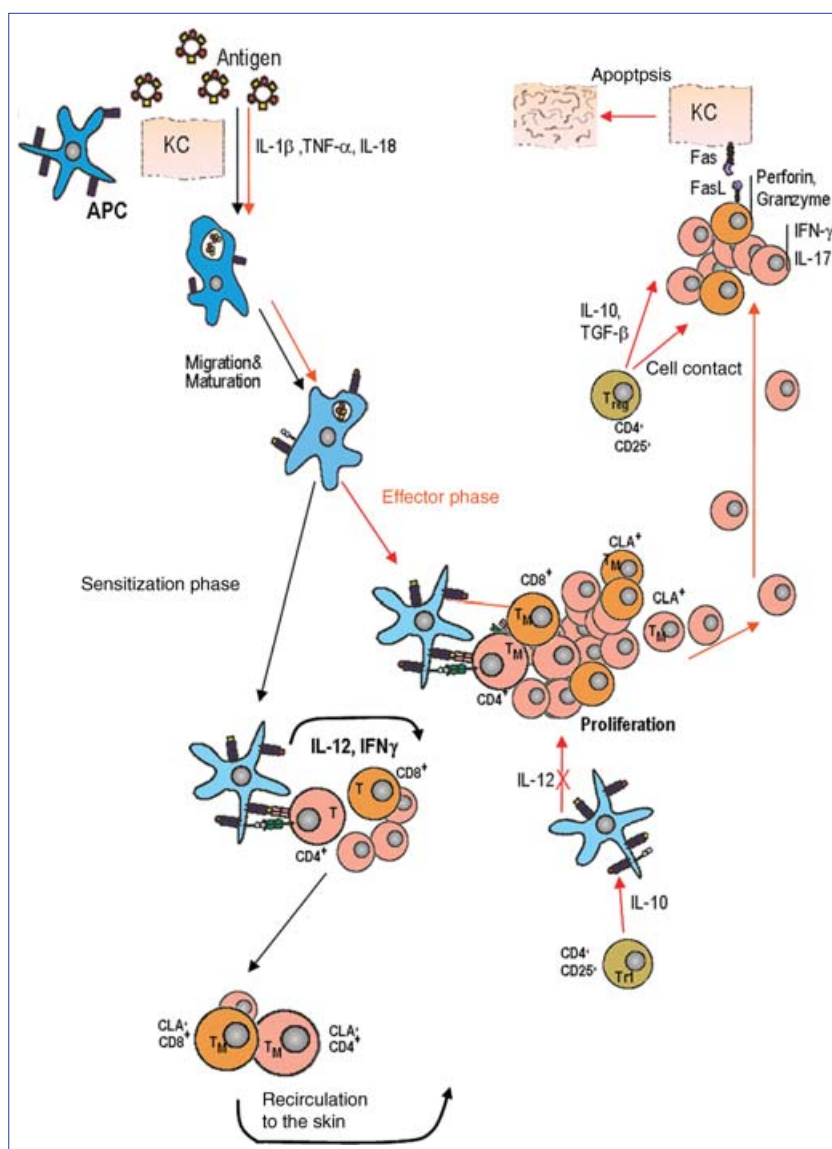


Figure 5: Development of a type IV allergy. APC (antigen-presenting cell), KC (keratinocyte), CLA (cutaneous lymphocyte-associated antigen), T_M (memory T cell), T_{reg} (regulatory T cell), T_{H1} (regulatory T_{H1} cells).

leading to recruitment of antigen-specific memory T cells from the blood. This leads to early arrival of Tc1 CD8⁺ T cells and CD4⁺ Th1 cells. T-cell cytokines such as IFN- γ and IL-17 cause stimulation of keratinocytes, which in turn secrete multiple cytokines and add to the inflammatory reaction by recruiting additional leukocytes. Keratinocytes are the main target cells of Tc1 (cytotoxic) CD8⁺ T cells, which are driven into apoptosis by interaction with Fas ligand on Tc1 CD8⁺ T cells and under the influence of their lytic granules (perforins and granzymes). The migration of antigen-specific Th2 CD4⁺ T cells does not occur until later. These cells provide anti-inflammatory mechanisms such as secretion of IL-10, thus avoiding tissue damage and ultimately restoring tissue integrity. Among these cells are IL-10-producing type 1 Tr cells (Tr1) which inhibit dendritic cell functions. A subset of CD4⁺ T cells express CD25 and possess immunoregulatory functions (T_{reg}) via secretion of IL-10 and TGF- β (as well as direct cell-cell contact. Up to 20 % of people who do not react to nickel with eczema have these cells in T-cell infiltrate which can inhibit allergen-specific T-cell responses (Figure 5).

Conflict of interest

None.

Delayed migration of CD4⁺ T cells provides a regulatory mechanism that stops the inflammatory reaction, avoids tissue damage, and restores tissue integrity.

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References

- 1 Wegen des Formates der Rubrik sind keine speziellen Referenzen angegeben, sondern generelle Übersichtsarbeiten und Einzelarbeiten aufgelistet.
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Fragen zur Zertifizierung durch die DDA

1. Welche Aussage ist richtig?

- a) Angeborene Immunität wird nur von humoralen Abwehrmechanismen vermittelt.
- b) Angeborene Immunität wird nur von zellulären Abwehrmechanismen vermittelt.
- c) Adaptive Immunität wird ausschließlich von Antikörpern vermittelt.
- d) Angeborene und adaptive Immunität werden von verschiedenen humoralen und zellulären Abwehrmechanismen vermittelt.
- e) Adaptive Immunität spielt für die Entwicklung von Allergien keine Rolle.

2. Für Mustererkennungsrezeptoren (PRRs) gilt:

- a) PRRs werden nur auf dendritischen Zellen exprimiert.
- b) Zu den PRRs zählen ausschließlich Toll-like-Rezeptoren.
- c) Stimulatoren sind Lipopolysaccharide, Peptidoglycan und nichtmethylierte CpG-Abschnitte in bakterieller DNA.
- d) PRRs unterliegen einem klonalen Rearrangement.
- e) PRRs werden nicht auf Keratinozyten und Fibroblasten exprimiert.

3. Welche Aussage ist richtig? Das Komplementsystem besteht aus:

- a) Antikörpern
- b) MHC-Komplexen
- c) Immunkomplexen
- d) Plasmaproteinen und stellt ein komplexes Immunsystem dar
- e) Membranrezeptoren

4. Für den MHC gilt:

- a) Proteine des MHC fungieren als Restriktionselemente bei der Interaktion von T-Zellen und Antikörpern.
- b) MHC wird nur auf T-Zellen exprimiert.
- c) MHC besteht aus Proteinen, die die Präsentation von Antigen an zytotoxische CD8⁺ T-Zellen und an CD4⁺ T-Helferzellen vermittelt.
- d) MHC kann keine Peptide binden.

- e) MHC spaltet Antigene in Peptidfragmente.

5. Welche Aussage ist richtig? Antikörper ...

- a) werden hauptsächlich von T-Zellen produziert.
- b) sind Bestandteil der angeborenen Immunität.
- c) vom Typ IgE binden über Fcγ-Rezeptoren an Mastzellen.
- d) können kein Komplement binden.
- e) einer Untergruppe können nur jeweils von einer B-Zelle produziert werden.

6. Für die Differenzierung naiver CD4⁺ T-Zellen gilt:

- a) Zytokine spielen im Allgemeinen keine Rolle.
- b) Eine Th2-Differenzierung ist in der frühen Phase der Entwicklung einer Typ-I-Allergie bedeutsam.
- c) Regulatorische T_{reg} verstärken CD4⁺ T-Zell-Effekte.
- d) Differenzierte CD4⁺ Th2-T-Zellen sezernieren kein IL-4, IL-5 und IL-13.

Nur differenzierte CD4⁺ Th2-T-Zellen binden IgE über Fc-Rezeptoren.

7. Welche Aussage ist richtig? Bei der allergischen Reaktion vom Soforttyp (Typ I) ...

- a) ist keine vorherige Sensibilisierung nötig.
- b) sind Mastzellen wichtige Effektorzellen der frühen allergischen Typ-I-Reaktion.
- c) entfaltet Histamin seine Wirkung hauptsächlich über H2-Rezeptoren.
- d) spielen eosinophile Granulozyten und Th2-Zellen keine Rolle.
- e) differenzieren keine langlebigen Memory-Zellen.

8. Für die allergische Reaktion vom Typ II gilt:

- a) Humoral zytotoxische Immunreaktionen werden durch IgE-Antikörper vermittelt.

- b) Humoral zytotoxische Immunreaktionen sind bei Arzneimittelallergien bedeutsam.
- c) Humoral zytotoxische Immunreaktionen sind gegen lösliches Antigen gerichtet.
- d) Komplementvermittelte Zytolyse spielt keine Rolle.
- e) Antikörperabhängige zellvermittelte Zytotoxizität (ADCC) ist nicht bedeutsam.

9. Welche Aussage ist richtig? Die Allergische Reaktion vom Typ III ...

- a) wird durch Antikörper vermittelt, die gegen lösliche Antigene gerichtet sind.
- b) tritt in einem Zeitintervall von 24–72 h auf.
- c) findet vor allem in Organen mit vergleichsweise niedriger Durchblutung statt.
- d) wird ohne Bildung von Immunkomplexen vermittelt.
- e) löst keine Entzündungsreaktion durch Fcγ-Rezeptoren auf Leukozyten sowie durch Komplementaktivierung aus.

10. Welche Aussage ist **nicht** richtig?

- a) Die Immunreaktion vom verzögerten Typ beruht auf der Aktivierung von antigenspezifischen Tc1-CD8⁺ T-Zellen und CD4⁺ T-Zellen.
- b) Die Immunreaktion vom verzögerten Typ benötigt 24–48 h bis zur Ausprägung.
- c) Die allergische Kontaktdermatitis wird häufig durch niedermolekulare Substanzen, sogenannte Haptene, ausgelöst.
- d) Keratinozyten sind bei der allergischen Kontaktdermatitis nicht betroffen.
- e) Tc1-CD8⁺ T-Zellen führen Zielzellen mittels lytischer Granula (Perforin und Granzyme) in die Apoptose.

Liebe Leserinnen und Leser,

der Einsendeschluss an die DDA für diese Ausgabe ist der 14. Dezember 2007.

Die richtige Lösung zum Thema „Literaturbewertung mit Instrumenten der evidenzbasierten Medizin: eine Einführung anhand einer dermatologischen Therapiestudie“ in Heft 9 (September 2007) ist:

1d, 2c, 3b, 4b, 5e, 6d, 7d, 8a, 9c, 10e.

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