Immunopathology of allergic contact dermatitis *

Imunopatologia da dermatite de contato alérgica

Luis Eduardo Agner Machado Martins [1] Vitor Manoel Silva dos Reis [2]

Abstract: Allergic contact dermatitis is the consequence of an immune reaction mediated by T cells against low molecular weight chemicals known as haptens. It is a common condition that occurs in all races and age groups and affects the quality of life of those who present it. The immunological mechanism of this disease has been reviewed in recent decades with significant advance in its understanding. The metabolism and pathway of the haptens as well as the activation and mechanism of action of the cells responsible for both the immune reaction and its completion are discussed in this article.
Keywords: Allergy and immunology; Dermatitis, allergic contact; Dermatitis, contact; Hypersensitivity

Resumo: A dermatite de contato alérgica é consequência de uma reação imune mediada por células T contra químicos de baixo peso molecular, denominados haptenos. É uma condição frequente que ocorre em todas as raças e faixas etárias e afeta a qualidade de vida de seus portadores. O mecanismo imunológico desta doença vem sendo revisto nas últimas décadas com significativo avanço no seu entendimento. A metabolização e o caminho dos haptenos, bem como a formação e o mecanismo de ação das células responsáveis tanto pela reação quanto pelo seu término, são discutidos neste artigo.
Palavras-chave: Alergia e imunologia; Hipersensibilidade; Dermatite de contato; Dermatites alérgicas de contato

INTRODUCTION

The skin is the organ that separates the human body from the external environment. This function exposes it to physical, chemical, and biological aggression that determines diseases such as eczema. Eczema is a form of dermatitis characterized by the presence of erythema, edema, vesicles and exudation (acute eczema); pink erythema and desquamation (subacute eczema) and lichenification (chronic eczema). Eczema caused by exogenous agents whether contactant or endotantes are called contact eczema or contact dermatitis (CD). Contact dermatitis can be caused by irritants, irritant contact dermatitis (ICD), or sensitizers, allergic contact dermatitis (ACD). ICD results from exposure to agents that cause direct tissue damage, such as acids and alkalis. As for ACD, it results from a specific immune response against the contactant in people previously sensitized. The immune reaction against the antigen, which is generated to destroy it, causes tissue damage.[1]

When triggered by exposure to sunlight, CD can be classified as phototoxic CD and photoallergic CD. Phototoxic CD presents the same mechanism as ICD, but requires sun exposure for the contactant to become an irritant and then trigger the dermatitis. Similarly, in photoallergic CD, sun exposure turns the inert contactant into an allergen, thus triggering the immune process.[1]

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[1] PhD in Dermatology - Volunteer Dermatologist at the Federal University of Parana (UFPR) – Curitiba (PR), Brazil.
[2] PhD – Dermatologist at the University of Sao Paulo – Sao Paulo (SP), Brazil.

EPIDEMIOLOGY

CD is a universal, frequent disease which is responsible for about 10% of the visits to dermatology offices. [2] It affects all ages and ethnicities, but its incidence is lower during childhood, due to less exposure to more sensitizing substances, and in blacks, due to particularities of the skin of this group. [3,4]

The socioeconomic impact of CD is great, but difficult to quantify. Occupational CD represents one of the most prevalent occupational diseases and is considered a public health problem.[5] It corresponds to more than 90% of the occupational dermatitis, especially in developing countries where industries do not always adopt all necessary protection measures and is responsible for about one quarter of all absences from work.[6-8]

Besides frequent, CD affects the quality of life of the individuals who suffer from it. Itching, pain, exudation and possible infection of the lesions compromise the patients' social and professional life as well as their rest.[8,9] The discovery of the agent responsible for CD changes its evolution and prognosis, thus improving quality of life. [9, 10]

There are over 3,700 substances that can trigger ACD. Prevalence of ACD by a particular antigen depends on its sensitizing potential and the frequency and duration of exposure to it. The conditions of exposure are also important, since they may favor the development of sensitization. Occlusion, moisture and contact of the allergen with the damaged skin favor its penetration and sensitization.[11,12] Prevalence of ACD in various populations differs, since it results from the peculiar antigenic exposure of each region.[13] Furthermore, the rate of sensitization of a given population is constantly changing, as presence and exposure to sensitizers change over time.[14]

IMMUNOPATHOLOGY

The sensitization mechanism is quite complex and, despite being the object of numerous studies, it is only partly known. Recent decades have witnessed a rapid advancement in the understanding of allergic contact response, this progress occurred in parallel with findings about the immune system and the development of tools to study it. Various research techniques, applied mostly in experimental models with mice, such as the development of monoclonal antibodies (which allowed the identification of cells and cytokines by different methods), cell cultures, administration of cytokines, inactivation of genes *("knock-out")*, among others are responsible for the advances to be discussed.

ACD is an inflammatory disease triggered by haptens and mediated by T cells.[15] Haptens are small reactive molecules with molecular weight below 500 Da which are not immunogenic by themselves, but which bind to peptides and proteins, thus becoming recognized by the immune system.[16] In 1935, Karl Landsteiner and John Jacobs[17] wrote about the existence of reactive chemicals of low molecular weight that bind to proteins and then determine the formation of antibodies or antibody-like substances, supposedly responsible for ACD. Only 40 years later, Shearer[18] demonstrated that hapten-specific T lymphocytes (TL) also respond to these hapten-protein complexes.

ACD occurs as a result of a cascade of physicochemical and immune processes that can be didactically divided into two phases: induction, also called afferent, and elicitation or efferent. The induction phase involves all of the steps, from the initial contact with the allergen to the development of sensitization. Elicitation begins after contact with the hapten in a previously sensitized individual and results in ACD. Figure 1 summarizes the events involved in these phases.[19,20]

AFFERENT PHASE

The afferent phase develops over time as a result of repeated exposure to environmental agents. Most of the contactants are too large to pass the stratum corneum, but haptens, due to their low molecular weight, penetrate this layer and spread toward the basal layer without being recognized by the immune system. During this diffusion process, they bind to tissue proteins and become immunogenic. The inherent reactivity of haptens is due to the non-pairing of electrons in the last layer of these molecules. They usually bind through covalent bonds to the amino acids of tissue proteins to stabilize them.[12] Several nucleophilic (electron rich) amino acids react with electrophilic (electron poor) haptens, donating electrons to these molecules. Among these, some notable amino acids are lysine and cysteine, but others such as histidine, methionine and tyrosine also perform this action.[12] Proteins, to which the haptens bind, can be derived from keratinocytes, components of Langerhans cells (LC) or peptides previously processed and bound to MHC class I or II. [21] The nature of the hapten, the type of binding of the hapten to its carrier and the final three-dimensional configuration of the complex formed influence the immunogenicity of the hapten-protein complex.[22] Lipophilic haptens can penetrate LC and bind to cytoplasmic components of these cells, which are processed by proteosomes and bind to MHC class I to be presented to CD8 TL. In contrast, hydrophilic haptens tend to combine with extracellular tissue proteins and are captured by LC, processed and bound to

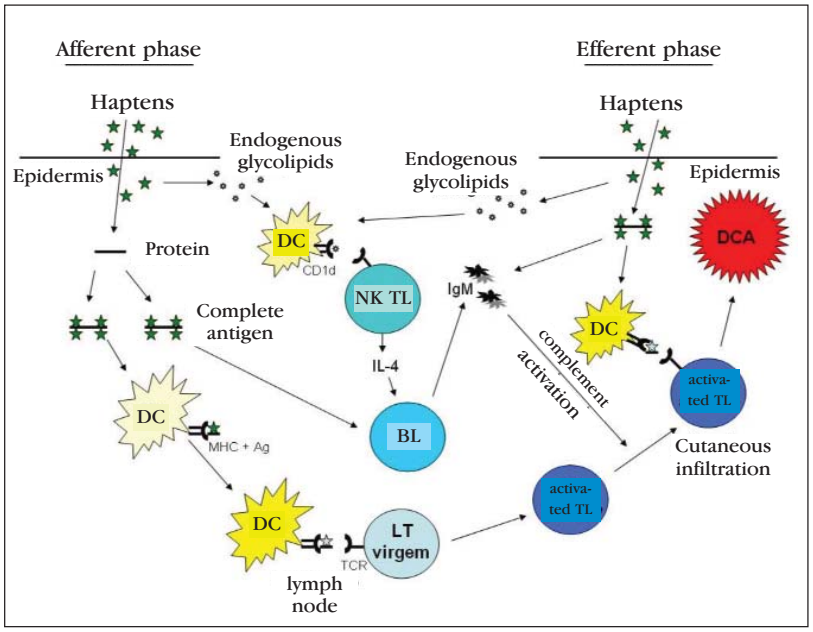

Figure 1: Mechanism of sensitization and elicitation of allergic contact dermatitis. In the afferent phase, haptens penetrate the skin and bind to tissue proteins becoming complete antigens (Ag). These antigens are captured and processed by dendritic cells (DC), which present them bound to MHC molecules on the surface of the cell membrane. DC migrate to regional lymph nodes where they present the antigen to TL. The TL that recognize the antigen presented are activated. The penetration of antigens into the skin also determines the release of endogenous glycolipids, which are presented by DC to NK T lymphocytes (NK TL). The NK TL release IL-4, which stimulates type 1 B lymphocytes to produce IgM. Faced with a new contact, the interaction of the IgM with the antigen-protein complex leads to activation of the complement, which induces the release of inflammatory and chemotactic factors of mast cells and endothelial cells. The activated TL migrate to the skin and interact with DC and keratinocytes that carry the antigen, thus leading to ACD

Adapted source: by Gober and Gaspari[19] and Campos et al[20]

MHC class II molecules to be presented to CD4 TL. [21] The peptide-MHC complex is expressed on the surface of the dendritic cell (DC), enabling the presentation of the antigen to hapten-specific T lymphocytes in the regional lymph node.[22-24]

LC originate from $CD34^+$ cells derived from bone marrow and reach the skin through the bloodstream.[25] These cells remain in the epidermis in an immature state, extremely able to capture and process antigens but unable to present them and form effector cells.[26] Capture of antigens promotes a series of morphological and functional changes in the DC. They become more dendritic, increase the number of Birbeck granules and costimulatory molecules, produce greater amounts of cytokines and change the profile of chemokine receptors in their membranes. Among the cytokines are the pro-inflammatory cytokines IL-1β and TNF-α.[27,28] IL-1b cytokines released by LC cause keratinocytes to produce TNF-α and GM-CSF, which together with IL-1β determine the maturation and migration of DC to lymph nodes.[29,30]

IL-1β and TNF-α transform the DC, which change from cells that are ready to capture and process antigens to cells that specialize in antigen presentation.[31] IL-1β increases the expression of costimulatory molecules such as ICAM-1 and CD86 in DC, which are needed for the activation of hapten-specific effector TL.[32,33] TNF-α acts at several points in the migration of DC: a) decreases the expression of E-cadherin in LC, a molecule that promotes the adhesion of these cells to keratinocytes, b) induces the release of metalloproteinases that degrade the basement membrane, c) promotes the interaction of adhesion molecules, such as LFA-1, ICAM-1 and VLA-6 of the DC, with the dermal matrix, d) increases the expression of CCR7, a receptor that responds to chemokines of the secondary lymphoid tissue.[21,34-37] These changes lead to the migration of DC towards the endothelium of the afferent lymphatic vessel in response to the gradient of chemokines produced by these cells. Pro-inflammatory cytokines, IL-1 and TNF-α, increase the expression of E-selectin and VCAM-1 in endothelial cells.[38,39] The interaction between Sialyl Lewis X, a selectin whose expression is increased in DC during allergic reactions, and its ligand, E-selectin of endothelial cells, promotes the passage of DC to lymph nodes.[15,34,40,41]

Within twenty-four hours after contact with the antigen, DC migrate to regional lymph nodes for antigen presentation.[42] In the paracortical area of regional lymph nodes, DC meet and touch several naive T lymphocytes that are in the process of recirculation. The nature of these dendritic cells enables multiple cellular contacts favoring cell activation. Naive lymphocytes also express CCR7 which directs them to the same place.[43] DC remain in the paracortical zone with the aid of EBI1-ligand chemokine, which is produced by resident mature DC and also binds to CCR7.[44] To activate naive T cells, DC must pass two signals.[45] If the lymphocyte has the complement receptor to the pep-

tide-MHC complex, it will receive the first signal. The first signal determines conformational changes in the co-stimulatory molecules of the naive TL making them more eager for their ligands that are present in DC. Also, the first signal leads to transcription of IL-2 mRNA; however, the mRNA formed is unstable.[46] The second signal is given by the connection between costimulatory molecules of DC, ICAM-1, CD80 and CD86, and their respective ligands, LFA-1 and CD28 (which binds to both CD80 and CD86) in TL. CD86, when bound to CD28, stabilizes the IL-2 mRNA inducing TL to produce large amounts of this cytokine. Activated lymphocytes begin to express the complete receptor of IL-2, thus becoming susceptible to this cytokine, which by autocrine action leads to cell proliferation, a process known as clonal expansion.[46-48] Clonal expansion forms a large number of hapten-specific T cells which will respond to a future contact with the allergen. In the activation of T cells, in addition to the first and second signals, the cytokines produced by DC and present in the microenvironment where antigen presentation occurs also have an essential role. Cytokines determine the type of response to the antigen presented, the IL-12 leads to the formation of effector cells, while IL-10 determines the emergence of regulatory cells, cells that suppress the process.[49.50] After clonal expansion in the regional lymph nodes, the TL go to the thoracic duct and enter the bloodstream. These hapten-specific T cells express the cutaneous lymphocyte antigen (CLA), which preferably directs these lymphocytes to cutaneous inflammatory processes.

EFFERENT PHASE

To find the allergen, T cells must pass through the dermal microvasculature, the dermis and reach the keratinocytes modified by the antigen where they will act. This whole passage is regulated by chemokines and adhesion molecules expressed in tissues and recognized by TL.

The activated TL presents the homing antigen (CLA), VLA-4 and chemokine receptors.[50-54] CLA binds to the E-selectin expressed in the endothelial cells stimulated by the presence of antigen in the overlying skin, thus beginning the process of rolling. However, only when the VLA-4 or LFA-1 of leukocytes bind respectively to the endothelial integrins VCAM-1 and ICAM-1, a firm connection is formed, which combined with stimulation of chemokines allows diapedesis.[38.55-57] As the expression of ICAM-1 in the endothelium only increases 16 hours after contact with the antigen, period during which much of the influx of lymphocytes has already occurred, E-selectin and VCAM-1 appear to be particularly important early in the process and ICAM -1 in its amplification.[57]

Once in the dermis, the VLA-4 and VLA-5 of TL bind to fibronectin, an extracellular protein of the dermal matrix, which facilitates the transit of these cells in this medium.[58] Chemokines direct lymphocytes to the epithelium, and the connection between ICAM-1, expressed in keratinocytes, and the LFA-1 of leukocytes promotes interaction between these cells.[42] Lymphocytes produce a vigorous inflammatory response to eliminate the keratinocytes modified by the antigen. Only a small fraction of TL found in the ACD are hapten-specific.[59] These cells release large quantities of IFN-γ, which stimulates other T cells, NK cells and macrophages to migrate and expand the inflammatory process and which increases the expression of Fas in keratinocytes, making them more susceptible to FasL-mediated cytotoxicity.[60.61] Besides the Fas-FasL pathway, it has been shown that perforins also participate in the destruction of cells in contact dermatitis.[62] Keratinocytes undergo apoptosis, occurring cleavage of E cadherin, which results in loss of cell cohesion demonstrated by spongiosis and vesicles.[63] Tissue destruction and desquamation removes the antigen of the tissue, decreasing the inflammatory process.[15]

INVOLVED CELLS

Dendritic cells

The application of haptens to the skin induces successive extension and retraction of the dendrites of Langerhans cells (LC), as well as it induces the migration of these cells to regional lymph nodes.[64] These movements are stimulated by IL-1 and TNF alpha, cytokines produced by keratinocytes and by LC themselves after contact with the antigen.[65] These cytokines also induce maturation and migration of LC.[66] During the process of maturation, DC increase the expression of costimulatory molecules such as CD40, CD80 and CD86, adhesion molecules such as ICAM-1 and cytokines such as IL-12.[67-69] The maturation process is necessary for activation of naive hapten-specific T cells in regional lymph nodes for effector and memory TL.[70] The maturation described occurs upon exposure to haptens, whereas irritants, when applied to the skin, induce migration of LC, but not maturation, preventing the formation of a specific effector response. [69] The stimulated DC are attracted to the afferent lymphatic vessels, since they begin to express CCR7, which responds to the chemokines of the lymphoid tissue CCL19 and CCL21.[71] The afferent lymphatic vessels express CCL21 and the paracortical zone of lymph nodes express both CCL21 and CCL19, attracting DC to this region of the lymph nodes by the gradient of cytokines.[72] The role of DC in ACD has been recently revised, as we shall see below.

Dendritic cells in the afferent phase

There is controversy about the role of LC in the induction phase of ACD. Langerin is a transmembrane protein that leads to the formation of Birbeck granules, a specific marker of LC. Using a murine model where the injection of diphtheria toxin leads to selective depletion of cells expressing langerin, Bennett *et al.*[73] showed in May 2005 that the absence of LC decreases the chance of sensitization to haptens. The authors credited the sensitization of some of the mice exposed in the trial to dermal DC and found that these cells work together with LC in the sensitization process and that their absence affects this mechanism. However, in the same month, Kissenpfennig *et al.*[74] using a similar model found the same response to haptens between mice with depletion of LC and control groups of mice and concluded that LC are dispensable in the presentation of haptens, leaving this function to dermal DC only. In December of that same year, Kaplan *et al.*[75] demonstrated that mice that constitutionally do not present LC have increased response to haptens, that is, according to this model LC have a regulatory role. Until then the role of LC in sensitization had been defined as inducer, indifferent or suppressor. In 2007, Bennett e*t al.*[76] returned to their model and demonstrated that antigens are not properly transported to lymph nodes in the absence of LC and concluded that it decreases sensitization to antigens, confirming their findings in the first trial. They attributed the following to the differences found in the other studies: 1) perennial absence of LC in the model of Kaplan et al. and 2) the use of high concentrations of allergens in the other studies. In their immature state, LC carry self-antigens to the lymph nodes, generating tolerance mechanisms such as regulatory T cells.[77,78] The absence of these cells may have prevented the development of this mechanism and led to a state of hyperreactivity, responsible for increasing sensitization to haptens. Concerning the use of high concentrations of allergens, the authors report that they do not reflect usual exposure, but the artificiality of the models created, which might have generated an alternative response pathway.[76,78] Later, Fukunaga *et al.*[79] demonstrated that mice with a defect in migration of LC to regional lymph nodes but with normal migration of dermal DC present normal response to haptens, thus suggesting that dermal DC are more important in generating an effector response against haptens than LC. All these data clearly demonstrate that dermal DC are able to determine an effector response to haptens, but they do not allow a proper conclusion about the role of LC.

A new subtype of langerin DC has been recently described: langerin dermal DC.[80] These cells are not LC in transit to regional lymph nodes, for they come from a different lineage of cells; when depleted, they are able to repopulate tissues much faster than LC and, despite being phenotypically very similar, they have their own surface markers.[80-82] Langerin dermal DC also capture and present antigens. Using a model of selective ablation of LC and langerin dermal DC, Wang *et al.*[83] demonstrated that an attempt of sensitization immediately following depletion, a time period characterized by the absence of both LC and langerin dermal DC, is frustrated, but when performed some days after ablation, when part of the langerin dermal DC have already returned but LC have not, response to sensitization is normal. That trial indicates that langerin dermal DC and not LC and langerin dermal DC are the main responsible for the development of ACD. However, Bursch *et al.*[80] and Bennett *et al.*[76] used a similar system and failed to induce ACD with low concentrations of oxazolone in the fourth week after ablation, time period during which only langerin dermal DC have returned to normal, indicating that LC are necessary for sensitization. A possible conciliatory explanation lies in the concentration of haptens applied to sensitization. Bacci *et al.*[84] and Bennett *et al.*[76] suggest that at higher concentrations the antigen is captured by both LC and dermal DC, which induce the generation of an effector response in regional lymph nodes, and that at lower concentrations the antigen is especially captured by LC, which induce the process by themselves.

Dendritic cells in the efferent phase

Clear evidence indicates that LC are not required in the elicitation phase. Induced depletion of these cells by topical corticosteroids, UVB radiation or their selective ablation in experimental models with previously sensitized mice did not result in reducing the allergic response.[73,74,76,85] It is believed that macrophages, keratinocytes and mast cells also act as antigen-presenting cells.[86,87] The role of these presenting cells, including LC, in the effector phase of ACD is still under study.

LYMPHOCYTES

Effector lymphocytes

ACD was considered the prototype of delayed type hypersensitivity (DTH) for a long time; however, the subpopulations of lymphocytes and the antigens involved in ACD present peculiarities which individualize this reaction.[21] In DHT, the antigens are relatively large and soluble proteins, whereas they are small, reactive and lipophilic compounds in contact sensitization.[21] The primary effector cell in DHT is CD4 TL while the main effector cell in ACD is CD8 TL, which has its action supported by type 1 auxiliary TL and

suppressed by other CD4 T cells.[47, 88] A series of findings, described below, led to these conclusions.

Gocinski *et al.*[89] demonstrated that mice with depletion of CD8 TL induced by anti-CD8 monoclonal antibody are unable to develop ACD. However, mice with induced depletion of CD4 TL develop more intense and prolonged clinical response to the allergen. Similar results were obtained with mice with "knockout" (inactivation) of MHC class I and II. The absence of these molecules prevents the activation of CD8 TL and CD4 TL respectively, leading to the same consequences as those of selective absence of these subpopulations of lymphocytes.[90]

In a sequential evaluation of the inflammatory infiltrate of ACD, Okazaki *et al.*[91] showed that the lymphocytes found at the beginning of the process are CD8 TL that produce IFN-γ followed by CD4 TL. The highest proportion of CD8 TL was found 12 hours after contact while the highest proportion of CD4 was found after 24 hours.

In 1998, Cavani et al. [92] showed that only individuals who are allergic to nickel present antigen-specific CD8 TL (Tc1). However, antigen-specific CD4 T cells are found in allergic and non-allergic individuals, differing only in relation to highest proportion of suppressor cells, producers of IL-10, in the sound group.[50] IL-10 inhibits the differentiation and maturation of DC, blocking the release of IL-12, which is necessary for generating an allergic response.[92]

Despite the mounting evidence that the main effector cell of ACD is CD8 TL, it is possible that the nature of the antigen and/or its access pathway may contribute to determining the cell type involved in the response that will be formed.[21,93]

Besides the IFN-γ-producing CD8 TL and CD4 TL, Th17 lymphocytes also exert an important effector role in ACD. Th17 cells are effector T lymphocytes that express factor ROR-γt (a variant of the orphan receptor related to retinoic acid) in mice and its equivalent (RORC) in humans. These cells produce proinflammatory cytokines such as IL-17, IL-21 and IL-22 and the chemokine receptor CCR6, which directs these cells to the epithelium for defense against bacterial and fungal infections.[59] When stimulated by contact with haptens, human keratinocytes produce IL-23, which together with IL-1 beta leads to the development of Th17 lymphocytes.[94] Individuals with contact sensitivity present Th17 lymphocytes in peripheral blood that respond to the antigen-presenting cells that carry the allergen. [94] In addition to Th17 lymphocytes, Tc17 lymphocytes were also found in the tissue cellular infiltrate.[59] The main actions of IL-17 produced by these cells are induction of proinflammatory cytokines (such as IL-1, IL-6 and TNF-α), chemokines (CXCL1, CXCL2, CXCL5 and CXCL8) and adhesion molecules (ICAM-1 and VCAM-1) by epithelial and endothelial cells, thus leading to the recruitment of inflammatory cells and interaction of these cells with the epithelium.[59,95] This way, IL-17 increases the local inflammatory process.[95-97] An experimental model showed that the absence of IL-17 in mice compromises the development of contact hypersensitivity reaction, reinforcing the importance of these cells in contact sensitivity.[98]

Surprisingly, the NK cell was identified as the effector cell of ACD through *dinitrofluorobenzene* in mice with *knock-out* of Rag-2 gene, essential for the development of B and T lymphocytes.[99] This finding is notable, since it suggests that NK cells, despite not having T-cell receptors, are able to recognize specific antigens and develop memory.

REGULATORY T LYMPHOCYTES

Although ACD is a common condition, its occurrence is not the usual response resulting from the interaction of the cutaneous immune system with environmental chemicals. Most individuals are daily exposed to various chemicals and still do not develop contact allergy. The reaction is actually an uncontrolled response of the immune system to haptens.[100] The control of immune response to environmental chemicals is a priority task of the immune system and a series of mechanisms ensure homeostasis.[100] The interaction between DC loaded with hapten and antigen-specific TL usually results in apoptosis, anergy or induction of T cells with regulatory activity.[101] Loss of these mechanisms of tolerance leads to ACD.

The knowledge of regulatory T cells has been reviewed in recent years. These cells comprise a heterogeneous subfamily of T lymphocytes that suppress immune response by releasing inflammatory cytokines, especially IL-10, or by inactivating effector T cells through cell-cell contact via CTLA-4 (cytotoxic T lymphocyte antigen-4).[102] There are three types of regulatory cells that have been well studied in terms of contact sensitivity; CD4CD25 Treg cells, regulatory T cells 1 (Tr1) and Th3 lymphocytes.

Tr1 cells produce large amounts of IL-10, moderate amounts of IL-5 and TGF-β and do not produce IL-4 and IFN-Á. In vitro, these cells restrict differentiation and production of IL-12 by DC, inhibiting the formation of effector and memory cells.[50,103] These effects are mediated by IL-10 and result in the suppression of hapten-specific CD4 and CD8 T cells. Cavani et al.[92] showed that peripheral CD4 TL in individuals not allergic to nickel express greater amount of IL-10 and less of IFN-γ compared with allergic patients, that is, non-allergic individuals have a higher amount of hapten-specific Tr1 cells in the blood. Hapten-specific Tr1 cells can also be found in skin lesions of contact sensitivity where they modulate the

end of the process. [50.103]

The second type of regulating cell that has been well studied expresses the CD4 molecule, the alpha chain of the IL-2 receptor (CD25), cytotoxic T lymphocyte antigen-4 (CTLA-4) and the transcription factor Foxp3. These cells are called CD4CD25 Treg lymphocytes or Tregs.[104] They can also express CLA, presumably after an encounter with DC in regional lymph nodes, and migrate to the skin.[105] These cells are involved in tolerance to CLA and are also able to inhibit in vitro activation of effector cells exposed to the sensitizer of non-allergic individuals, but not of allergic patients.[106.107] The mechanism of suppression induced by these cells is still under debate. In vitro studies suggest the need for cell-cell contact by interaction of the CTLA-4 of the regulatory cell with CD80 and CD86 for inactivation of effector TL.[108] On the other hand, in vivo models indicate suppression mediated by the action of cytokines, especially IL-10.[109]

It is possible that regulatory T cells work in a cooperative system, since it has been shown that Treg cells induce the production of IL-10 in Tr1 cells.[110] These two types of regulatory cells present a wide range of chemokine receptors, such as CCR4 and CCR8, and are attracted by chemokines produced in the late phase of ACD, such as CCL1.[111.112] Thus, they act both in the afferent and efferent phase, preventing the emergence of allergy and minimizing the intensity and duration of the process when it has already been developed.

The mobilization and maturation of DC are promoted by exposure to signs of danger such as cell damage, UVB radiation, bacterial and viral products.[100] The state of maturation of DC determines the ability of these cells to direct naive hapten-specific TL to effector, memory or suppressor hapten-specific TL.[101] Naive CD4 T cells when stimulated with immature or partially immature DC in the presence of TGF-β may transform into CD4CD25 Treg lymphocytes.[113] Differentiation for Th1 or Tc1 lymphocytes depends on the production of IL-12 by DC, which occurs only when maturation is complete. [101.114] The coexistence of signs of danger and exposure to chemicals appears to be an important factor in the loss of tolerance to haptens. This way, the irritant effect, a characteristic of the most sensitizing contact allergens, may help break the mechanism of tolerance and together with the allergen determine the complete maturation of DC and induce the development of ACD.[115] A recent study confirms the importance of the irritant potential of a chemical in its sensitizing capacity.[116] The irritating action leads to high levels of IL-1b, IL-6 and low levels of IL-10, promoting the maturation of DC. [116] Haptens at low concentrations have their irritant effect reduced and may lead to the formation of hapten-specific T cells that produce IL-10, generating tolerance.[117]

The route of contact with allergens also determines the response pattern presented. Contact with mucous membranes determines the formation of TGF-b-producing T cells, known as Th3 lymphocytes, which also act as regulatory cells.[118.119] But total and persistent oral tolerance is only achieved in individuals who are not sensitive to the antigen in question and encounter the antigen for the first orally.[120] A simple prior contact with the antigen, even if there is no development of ACD, can prevent formation of tolerance. [121] Oral contact with the allergen leads to antigen presentation by other cells than the DC of the skin, favoring the formation of regulatory cells (Th3 lymphocytes), anergic T cells or apoptosis of hapten-specific T cells due to absence of an appropriate second signal. [59]

In addition to these controlling mechanisms, Gorbachev *et al.*[122] demonstrated that there is apoptosis of dendritic cells in lymph nodes and that this mechanism also suppresses ACD. The authors showed that mice with depletion of CD4 cells or *knockout* of the gene responsible for FasL show higher permanence of dendritic cells in lymph nodes compared with naive mice. The loss of apoptosis of the presenting cells resulted in intense and sustained activation of IFN-γ-producing CD8 TL in experimental mice. Besides these laboratory findings, the mice with depletion of CD4 cells or with altered FasL presented more intense and persistent clinical response to the allergen tested.

KERATINOCYTES

They are critical cells in the immune response of the skin due to their numerical dominance. keratinocytes are important for both inducing and controlling the response to haptens. The IL-1 receptors of keratinocytes respond to IL-1β released by LC exposed to the antigen producing TNF-α, which results in maturation and migration of LC.[123.124] The IFN-γ produced by TL increases the expression of ICAM-1 in keratinocytes, which binds to LFA-1 of lymphocytes, facilitating the infiltration of these cells into the epidermis and the process of antigen presentation.[125.126] Furthermore, IFN-γ increases the expression of MHC class II in keratinocytes.[126] This way, the keratinocytes can present the antigen to CD8 TL, since they constitutionally express MHC class I, and to CD4 TL, for they are induced to express MHC class II by IFN-γ. Under normal conditions, keratinocytes express low levels of the costimulatory molecules CD80 and CD86.[19] These molecules bind to their receptors in T cells (CD28/CTLA-4 - cytotoxic TL-associated antigen-4) and are necessary for leading to a second effective signal.[19] In the absence of a second

signal, the TL become anergic.[127.128] These anergic TL express a large amount of IL-2 receptors and therefore compete with effector and memory T cells for this growth factor. The contact of keratinocytes with allergens and irritants causes human keratinocytes to increase the expression of CD80, favoring the development of allergic contact response.[129] Moreover, as described above, keratinocytes promote the generation of Th17 lymphocytes by producing IL-1β and IL-23, which amplify the inflammatory process.

On the other hand, keratinocytes suppress DC by producing IL-10 in response to exposure to haptens.[130.131] Exposure to allergens also induces the production of IL-16, which is involved in the chemotaxis of CD4 TL, which suppress the inflammatory response.[132] They also produce PGE_2 and TGF-b. PGE_2 inhibits the production of proinflammatory cytokines.[133.134] TGF-b, in turn, blocks the action of activated T cells and prevents additional infiltration of leukocytes, since it reduces endothelial adhesion molecules.[135] Furthermore, keratinocytes in an inflammatory environment express high levels of the receptor activator of nuclear factor KB ligand (RANKL) that induces the expression of CD205 and CD86 in LC when it binds to the receptor activator of nuclear factor KB (RANK).[136] The expression of CD205 is associated with the induction of CD4CD25 cells, which suppress the immune response.[137]

Mast cells

Along with keratinocytes and endothelial cells, mast cells are an important source of TNF-α and act both in the afferent and efferent phase of contact hypersensitivity.[138] TNF-α is important to maturation of DC and passage of these cells through the endothelium. It also promotes infiltration of T cells, increasing the inflammatory reaction. Just as keratinocytes, mast cells have dual function, for they suppress ACD by producing IL-10.[139]

B lymphocytes and NK T cells

ACD was considered for a long time a process independent of the participation of B cells, but recent studies indicate an essential role of these cells in ACD in mice. In humans, this function is not yet established. B lymphocytes (BL) associated with ACD are type 1, which are B cells independent of T cells, do not form germinal centers, do not generally undergo DNA rearrangement and are a source of antigen-specific IgM.[140] This IgM is produced during the afferent phase of ACD, when type 1 BL proliferate rapidly.[141] Mice with depletion of type 1 BL have decreased ACD, which is restored with reposition of antigen-specific monoclonal IgM by transfer of type 1 BL from antigen-allergic donors or serum of mice 24 hours after their sensitization to the antigen in question.[141] IgM cleaves complement, thus forming C5a, which degranulates mast cells that release TNF-α among other factors. These factors, as well as the complement fractions, lead to vasodilation, increased expression of adhesion molecules in the local vascular endothelium and chemotaxis of leukocytes.[142.143] C5-deficient mice show reduced contact response to haptens.[144-146]

In turn, type 1 BL are activated by NK T cells, a subtype of lymphocyte that is part of the innate immune system. Despite presenting T-cell receptor, these cells do not undergo gene rearrangement and are able to connect, through this TCR, to highly conserved glycolipid bound to CD1d molecules, a molecule similar to MHC class I molecule, which is found in antigen-presenting cells.[19,147,148] The nature of this glycolipid remains unknown. After contact with this glycolipid, the NK T cell proliferates in the liver and releases cytokines such as IL-4, which is responsible for activating type 1 BL in the presence of the antigen.[46.149]

Molecular pattern-recognition receptors

The innate immune system uses different families of molecular pattern-recognition receptors to detect microorganisms and signs of danger.[150] There is already some evidence of the involvement of these receptors in ACD, since their mutations interfere with contact hypersensitivity response. No one knows for sure whether the haptens bind directly to NOD receptors or whether they induce the formation of endogenous ligands, but when this route is compromised, the efferent phase of ACD is also affected.[151] There is evidence that Toll-like receptors are also associated with ACD. Sensitization of mice deficient in TLR 2 and 4 or with concomitant deficiency of TLR 4 and of the function of IL-12, but not of TLR 4 or IL-12 alone, for 2,4,6-trinitro-1-chlorobenzene allergen is frustrated.[152]

Mechanism of allergic contact dermatitis by transition metals

Haptens can be classified as classical haptens, pro-haptens and transition metals. Classical haptens follow the route of lymphocyte activation described. Pro-haptens are chemicals that need to undergo some transformation to become reactive, as it occurs with urushiol and drugs.[153.154] Some authors prefer to divide these chemicals into pro-haptens, when the transformation occurs by an enzymatic process, and pre-haptens, when the process is not enzymatic and occurs through contact with environmental agents such as oxygen, heat and light. Transition metals are metals that tend to form compounds containing complex ions, compounds formed by a central metal ion surrounded by various ligands.[155] Nickel, chromium and

cobalt are examples of transition metals.[153.155] Unlike classical haptens, transition metals form ionic bonds with their carriers. Interactions between chemicals result from electrical connections between their atoms and are characterized by the energy needed to break them, which reflects its stability. Ionic bonds are considered weak because they need less energy to be undone and thus form less stable complexes compared with covalent bonds, a form of strong connection.

The bonds formed by transition metals are established with 4 to 6 electron-donating elements such as oxygen and nitrogen, forming geometric complexes well defined.[153.156] The lower stability of these complexes causes them to fall apart when they come into contact with another protein that has higher affinity with the metal, thus forming a new complex that is also reversible. This dynamic transfer and consequent formation of different complexes have hampered the characterization of the epitopes of metals.[157]

Another particularity of transition metals is the possibility of activating TL without processing the antigen, which was demonstrated by Moulon et al. using LC fixed with glutaraldehyde.[158] For activation of hapten-specific TL without antigen processing, the T cell receptor needs to approximate the MHC molecule of the antigen-presenting cell. This proximity forms a binding site with high affinity for nickel, which binds and stabilizes the complex by activating the T cell [153]

The skin barrier

Besides the nature and concentration of hapten, duration and frequency of the contact with the hapten, skin condition is also relevant in the process of sensitization.[159] As the haptens need to cross the stratum corneum, skin integrity is important to maintain homeostasis.[160] Presence of solution of continuity and local inflammatory process may contribute not only to the penetration of allergens but also to DC maturation, due to the presence of signs of danger in the affected skin. Moreover, mutations of filaggrin, which is necessary for the formation and compaction of the stratum corneum, seem to cause contact allergy predisposition.[161.162]

CONCLUSIONS

ACD is a complex process mediated by T cells, which is due to loss of tolerance to environmental chemicals. The advance in understanding cellular and molecular events seen in recent decades is dramatic. The mechanisms involved in loss of tolerance, the discovery of regulating and effector cells, the possible involvement of B cells, as well as the unveiling of the role of dendritic cells and cytokines involved in the process will enable the development of new therapies. ❑

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MAILING ADDRESS / ENDEREÇO PARA CORRESPONDÊNCIA:
Luis Eduardo Agner Machado Martins
Rua Marechal Deodoro, 869 – Conjunto 1101
80060-010 Curitiba (PR) – Brasil
E-mail: hd330@yahoo.com

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QUESTÕES

1. It is correct to state the following about ACD:
   a) It is caused by a limited number of allergens, around 30.
   b) It affects all ages, races and both sexes with the same frequency.
   c) The rate of sensitization caused by a given allergen is perennial and equal among the various populations.
   d) The discovery of the causative agent improves the patients' quality of life.

2. It is correct to state the following about ACD:
   a) ACD is a common and universal inflammatory disease, triggered by substances that cause direct tissue damage.
   b) Haptens are inert chemicals recognized by the immune system, which generates a response to eliminate them.
   c) Haptens are small reactive molecules that are not recognized by the immune system, but which bind to tissue proteins becoming immunogenic.
   d) ACD occurs at the first contact with the allergen.

3. It is correct to state the following about ACD:
   a) Haptens can be presented by both MHC class I molecules to $CD8^+$ TL and MHC class II molecules to $CD4^+$ TL.
   b) The reactivity of haptens is due to an excess of electrons in its last valence layer.
   c) Ionic bonds are the usual binding mode between haptens and proteins.
   d) The final three-dimensional configuration of the hapten-protein complex is irrelevant in its immunogenic potential.

4. It is correct to state the following about dendritic cells:
   a) Similarly to neurons, they are stellar-shaped and originate from the ectoderm.
   b) They are present in the skin ready for migration, antigen presentation and effector cell formation.
   c) The state of maturation and the migration of these cells are strongly influenced by IL-1,, TNF-α and GM-CSF which are released by dendritic cells and keratinocytes.
   d) Dendritic cells, when in contact with the antigen, send signals to the regional lymph nodes that activate hapten-specific TL.

5.With regard to the process of maturation and migration of DC, we can state the following about contact with the antigen:
   a) It increases the expression of costimulatory molecules (ICAM-1 and CD86) and the chemokine receptor of the secondary lymphoid tissue (CCR7).
   b) It causes morphological and functional changes in these cells, but does not change surface molecules.
   c) Selectins and integrins have a secondary role.
   d) The state of maturation of dendritic cells does not influence cell activation.

6. It is correct to state the following about the activation process of TL in ACD:
   a) The DC that carries the antigen is capable of activating a range of T cell receptors.
   b) Antigen presentation to the TL that presents a complement receptor to the allergen in question is sufficient for the formation of effector TL.
   c) Both the first signal (antigen presentation) and the second signal (binding between co-stimulatory molecules) are necessary for the formation of effector and memory T cells.
   d) IL-10 is produced by fully matured DC.

7. It is correct to state the following about ACD:
   a) During the afferent phase (induction) the cutaneous lymphocyte antigen (CLA) preferably directs TL to the skin.
   b) Binding of CLA to E-selectin of the endothelium is necessary and sufficient for diapedesis.
   c) Only a fraction of the TL found in ACD are hapten-specific; these cells attract other TL and immune cells that contribute to the inflammatory process.
   d) There is no participation of the Fas-FasL pathway in lesion of keratinocytes.

8. It is correct to state the following about ACD:
   a) Skin contact with irritants is incapable of leading to the migration of DC.
   b) Skin contact with irritants is incapable of leading to full maturation of DC, preventing the formation of effector and memory cells.
   c) Dermal DC are unable to induce sensitization in the absence of LC.
   d) Both LC and langerin-positive dermal DC are able to induce sensitization; the determination of which cell is responsible for the process depends on the quality of the antigen.

9. It is INcorrect to state the following:
a) LC are important in maintaining homeostasis because they generate tolerance.
b) LC are needed in the efferent phase.
c) IL-10 inhibits DC maturation, blocking the relea se of IL-12.
d) In addition to DC, macrophages, keratinocytes and mast cells can act as antigen-presenting cells in the efferent phase.

10. It is correct to state the following:
a) Contact sensitization is a typical form of delayed hypersensitivity reaction.
b) Delayed hypersensitivity reactions have $CD8^+$ TL as their main effector cell.
c) Mice with inactivation of the genes of the MHC class I show increased contact hypersensitivity reaction.
d) The first cells found in the inflammatory process of contact sensitivity are IFN-α-producing $CD8^+$ TL.

11. It is incorrect to state the following:
a) It is possible that the route of contact with the antigen and its nature determine the kind of effector cell.
b) In addition to IFN-γ-producing $CD4^+$ and $CD8^+$ TL, Th17 lymphocytes, but not Tc17 lymphocytes, are important in ACD.
c) IL-17 induces the expression of pro-inflammatory cytokines.
d) Mice unable to produce IL-17 show reduced contact response.

12. Mark the correct statement:
a) ACD is the usual response of the skin to repeated exposure to environmental chemicals.
b) Apoptosis, anergy and formation of regulatory T cells are irrelevant mechanisms in maintaining tolerance to haptens.
c) Sound individuals differ from ACD patients for having a higher proportion of IL-10-producing antigen-specific $CD4^+$ TL and not presenting hapten-specific $CD8^+$ TL.
d) The presence of signs of danger concurrent with antigen exposure favors the formation of suppressor cells.

13. Mark the incorrect statement:
a) There are three types of regulatory T cells involved in ACD: $CD4^+$ $CD25^+$ TL, Tr1 lymphocytes and Th3 lymphocytes.
b) Tr1 lymphocytes produce large amounts of IL-4.
c) Foxp3 is an important transcription factor in the formation of $CD4^+$ $CD25^+$ cells as well as it is used as their marker.
d) Regulatory T cells seem to work in a cooperative system.

14. Mark the incorrect statement:
a) The state of maturation of DC determines the kind of response that will be formed.
b) Fully matured DC express IL-10.
c) The irritating effect of chemicals seems to play an important role in loss of tolerance.
d) At low concentrations, haptens can lead to the formation of regulatory cells.

15. Mark the incorrect statement:
a) Oral contact with the antigen determines tolerance.
b) Oral contact with the antigen may determine tolerance only in non-sensitized individuals.
c) The apoptosis of DC in lymph nodes is also a controlling mechanism of contact response.
d) Mice with inactivation of the FasL gene present more intense and lasting ACD.

16. Mark the incorrect alternative in relation to keratinocytes:
a) They are cells of little relevance in the pathogenesis of ACD.
b)They respond to the IL-1b produced by LC producing TNF-α, which is important for maturation and migration of DC.
c) They respond to IFN-γ with increased expression of ICAM-1, which interacts with the LFA-1 of TL.
d) Keratinocytes present antigens by both MHC class I and II.

17. Mark the incorrect alternative in relation to keratinocytes:
a) In the absence of an irritant/allergic stimulus, the expression of the molecules CD80 and CD86 on the surface of keratinocytes is high, favoring the development of anergic hapten-specific T cells.
b) Anergic TL compete with effector and memory T cells for IL-2, an important growth factor of lymphocytes.
c) Keratinocytes promote the formation of Th17 cells by producing IL-1, and IL-23.
d) Keratinocytes release PGE_2 , which inhibits the production of inflammatory cytokines.

18. Mark the incorrect alternative:
a) Antibodies have an essential role in ACD in mice.
b) Antibodies related to ACD belong to the IgM class.
c) The antigen-specific antibody cleaves the complement.
d) C5a deficiency increases the response to haptens.

19. Mark the incorrect alternative:
    a) In mice, NK TL recognize endogenous glycolipids by their TCR.
    b) Glycolipids are presented bound to CD1d molecules present in antigen-presenting cells.
    c) The IL-4 released by NK T cells stimulates type 1 BL.
    d) NK T cells present the antigen directly to naive TL.

20. Mark the incorrect alternative:
    a) Pro-haptens are molecules that need to be metabolized to become reactive.
    b) The hapten-protein complex formed by transition metals is less stable than that formed by the other haptens.
    c) There is evidence of the involvement of molecular pattern-recognition receptors in ACD.
    d) Mutations in structural proteins of the skin do not seem to predispose to allergic contact.

Answers
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1. c	11. a	8. d
2. d	12. b	18. d
3. d	13. d	9. c
4. b	14. c	19. c
5. d	15. a	10. d
6. a	16. b	20. a
7. a	17. c	

Papers

Information for all members: The EMC-D questionnaire is now available at the home-page of the Brazilian Annals of Dermatology: www.anaisdedermatologia.org.br. The deadline for completing the questionnaire is 60 days from the date of online publication.