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Contact Dermatitis (A Gimenez-Arnau, Section Editor)

Immunological Mechanisms in Allergic Contact Dermatitis

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Abstract

Purpose of the review The understanding of the cellular and molecular pathogenesis of allergic contact dermatitis (ACD) has increased dramatically.
Recent findings Besides CD4+ and CD8+ T cells, other cell types such as innate lymphoid cells, natural killer T cells (NKT), natural killer cells, and T regulatory cells have emerged as crucial key players. New immunological insights have unravelled that the predominant effector cell type determines the clinical pictures. Hence, a better understanding of the involvement of distinct effector cells has shed light on the diversity of ACD reactions and subsequent clinical pictures. Another new perspective has arisen in the elicitation phase. Here, Langerhans cells can play a role in the development of immune tolerance and not, as previously thought, exclusively in the allergen-driven hypersensitivity reaction. B cells also appear to play an important role in triggering ACD by secreting IgM antibodies in response to interleukin (IL)-4 produced by NKT cells, leading to complement activation and chemotaxis of immune cells.
Summary Allergic contact dermatitis is a delayed-type hypersensitivity reaction triggered by skin contact with the chemical of interest in individuals previously sensitised to the same or a chemically related substance. The understanding of the cellular and molecular pathogenesis of allergic contact dermatitis has improved considerably. In addition to CD4+ and CD8+ T cells, other cell types such as natural killer T cells (NKT) and regulatory T cells have emerged as important participants. The binding of haptens is the first step in the development of allergic contact dermatitis. Haptens are low molecular weight (mostly <500 Dalton) chemicals that are able to penetrate the stratum corneum of the skin or can enter the body upon systemic administration. Haptens are not immunogenic per se but

can be effectively recognised by the immune system after binding to a protein carrier. In the clinically inapparent sensitisation phase, Langerhans cells and dendritic cells initiate an adaptive immune response by capturing and processing antigens and presenting them to naïve T cells in the paracortical regions of the lymph nodes. In the elicitation phase, the clinical manifestations of allergic contact dermatitis are the result of a T cell-mediated inflammatory response that occurs in the skin upon re-exposure to the bite and is mediated by the activation of bite-specific T cells in the skin or other organs.

Introduction

Allergic contact dermatitis (ACD) is a common inflammatory skin condition that often manifests as itchy, eczematous lesions. Other clinical presentations include a diversity of delayed-type drug hypersensitivity (DHR) reactions. ACD results from a T-cell-mediated delayed-type hypersensitivity (DTH) reaction triggered by skin or systemic contact with the chemical of interest in individuals who have been previously sensitised to the same chemical [1••]. ACD is common in the general population and is the most common occupational skin disease. The aetiology can be deduced from the affected body sites, the exposure history and the morphology and distribution of the skin lesions.

Hapten-protein interaction

The binding of haptens is the first step in the development of ACD. Most contact allergens are low molecular weight chemicals (< 500 Dalton) called haptens that are able to penetrate the stratum corneum barrier of the skin [1••]. An impaired skin barrier function, as often found in inflamed skin and, in particular, in atopic dermatitis, might enhance the penetration and, as a consequence, the sensitization risk. Haptens are not immunogenic per se, but can be effectively recognised by the immune system upon binding to an unspecific skin protein, called carrier [1••, 2]. The resulting complex is described as "hapten-carrier-complex". Haptens can be naturally occurring substances, such as plant extracts. Classical examples are urushiol, which is found in the resin of poison ivy, or natural fragrances. Other frequent haptens are synthetic compounds, such as preservatives or medicines.

Upon binding of haptens to skin proteins (protein haptenisation), either a strong covalent or a weaker non-covalent bond is formed. A covalent bond is formed between the electrophilic constituents of the hapten and the nucleophilic amino acid side chains of the target proteins in the skin [2]. Examples of chemicals with electrophilic constituents are aldehydes, ketones, amides or halogenated compounds. Metal cations (e.g. nickel [Ni]]2+, one of the most common ACD-associated haptens) are also known electrophiles. The most reactive nucleophilic side chains of proteins are located on lysine, cysteine and histidine. The nucleophilicity of proteins is influenced by the pH of the microenvironment and the position of the protein in the epithelium. Some haptens that are normally not electrophilic can be converted

into protein-reactive substances by oxidation or metabolic transformation by epidermal keratinocytes and/or dendritic cells. These haptens are called "pro-haptens". If a hapten requires activation outside the skin, for example, by oxidisation, the hapten is called "pre-hapten" [1••].

Other factors influencing the sensitising ability of haptens are lipophilicity, three-dimensional chemical structure and protein binding affinity. These factors are of particular importance by penetrating the stratum corneum and to pass through to deeper (epi)dermal layers in order to reach professional antigen-presenting cells. If a hapten enters the body by oral or systemic administration, similar mechanisms take place. They can occur either in the skin or other metabolic and immunological active organs such as the liver.

Sensitization phase

The sensitisation phase occurs after the first immunological relevant skin or systemic contact with a hapten and leads to the formation of hapten-specific T cells in the regional lymph nodes. Upon skin contact, professional antigen-presenting cells (APC) may be involved in the clinically imperceptible sensitisation phase. The APC belong to the innate immune system but are the key-players in initiating adaptive immune reactions by lymphocytes. In the skin, different APC subtypes have been identified. Among them, Langerhans cells (LC) and dermal dendritic cells (DC) are the best characterised. Immature DCs form a dense network in the epidermis and dermis where they scan the environment by extending and retracting their dendrites and take up antigens with high efficiency [3]. As professional antigen-presenting cells, LCs and DCs express class I and class II molecules of the major histocompatibility complex (MHC), which are required for CD8+ and CD4+ T cell activation, respectively. In case of systemic hapten exposure, other organ-specific professional antigen presenting cells, such as Kupffer cells in the liver, get involved.

LCs and other DCs are able to trigger an adaptive immune response by taking up antigens and processing them [3]. Another signal of efficient sensitisation is the generation of alarmins. These mediators signal the release of danger signals such as reactive oxygen species (ROS), ATP/ADP and damage-associated molecular patterns (DAMPs), such as hyaluronic acid fragments in particular urocanic acid [58, 59, 60]. These DAMPs are then recognised by pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs) on skin DCs, leading to their activation. Keratinocytes also produce a number of alarmins and cytokines which create a pro-inflammatory microenvironment in the skin that is necessary for the activation of the innate immune system.

Under the influence of this cocktail of soluble mediators released from surrounding keratinocytes and DCs themselves, DCs start to mature and to emigrate from dermal tissues via draining lymphatics towards the regional lymph nodes [1••]. After skin exposure to the sensitising agent, the density of epidermal LCs decreases by about 50% over the next 24 h as they migrate to the draining regional lymph nodes [3]. During migration, the LCs undergo a maturation process and acquire the surface phenotype of a functionally

mature dendritic cell. Cytokines released by keratinocytes, especially interleukin (IL)-1, tumour necrosis factor (TNF)-α and IL-18, regulate the migration and functional maturation of antigen-loaded dendritic cells. In addition to morphological changes and a decreased ability to take up additional antigens, mature DCs show increased expression of CD83 (a marker of DC maturation), adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), co-stimulatory molecules such as CD40, CD80 and CD86, and of chemokine receptors such as CCR7 [4]. The expression of CCR7 makes antigen-matured DC susceptible for the CCL-21-driven migration to and adhesion at the paracortical areas of the lymph nodes. In these regions also naïve T cells are located. Hence, the maturation induced expression of CCR7 facilitates the contacting of antigen-loaded DCs with naïve T cells at the cellular level. The regulation of DC maturation markers is specific to DCs exposed to immune response stimulating antigens. Skin irritants that also trigger LC migration do not result in similar changes in LC surface markers [5, 6]. The increased expression of signalling molecules on the cell surface of DC is important for the efficient activation of naive T cells in local lymph nodes.

The presentation of antigen by matured DC to naïve T cells is called immunological priming and, as far as known, irreversibly. It is the hallmark of adaptive immune responses in the sensitisation phase. This stimulation leads to a clonal expansion of hapten-specific T cells and the simultaneous formation of memory and effector/memory T cells that circulate throughout the body. The latter can be recruited from the circulation to the skin during the elicitation phase.

As learnt from mouse models, 24 h after sensitisation by cutaneous application of a strong allergen, mouse lymph nodes contain newly arrived LCs and can transmit sensitisation when implanted in allergen-naive mice [7]. However, studies in LC-depleted mice show that contact sensitisation is not abolished in the absence of LCs [8]. A population of Langerin+ dermal DCs could induce contact sensitisation in the absence of epidermal LCs, supporting the idea that LCs may be dispensable in ACD as there are other cutaneous antigen-presenting cells that can take over this function [9]. The exact interaction of the distinct APC types in men is yet far from understood.

At the end of the sensitization phase, hapten-specific T cells primed by hapten-loaded DCs are found in the lymph nodes, blood and skin. Upon re-exposure to the same antigen, the T cells are activated and recruited *en masse* in the skin ("elicitation phase").

Elicitation phase

The clinical manifestations of ACD are the result of a T-cell-mediated inflammatory response that occurs after re-exposure to the harmful hapten either in the skin or, upon systemic exposure, in a more generalised manner. This process is called elicitation phase and is mediated by the activation of hapten-specific T cells. As early as 10–14 days after the sensitization contact, an elicitation reaction can occur in men [10].

Upon later, renewed allergen contact, the inflammatory reaction occurs in general after 48 to 72 h after exposure. But, also much quicker reactions can be noted. They occur within hours and are called Jones-Mote reactions. Occasionally, very delayed reactions that appear later than 7 days after contact have been described. Therefore, the nature of allergen is important. Examples are neomycin that penetrates the skin very slowly, or corticosteroids that first suppress immune reactions. Another explanation of a very delayed immune response can be a very long delay after the last immunological relevant allergen contact. This can result in a lowered frequency of allergen-specific T cells.

As in the sensitisation phase, the haptens penetrate into the epidermis and react with endogenous proteins. These hapten-protein complexes are then taken up by APCs and presented to previously antigen-primed T cells, which are recruited to the epidermis and dermis. Interestingly, it has been found that recruited T helper (Th) 1 cells have produce significant amounts of the DAMP molecule extradomain A+ fibronectin, which is an endogenous ligand of TLR4. This leads to a positive feedback mechanism that further enhances immune activation in ACD [1••, 11••]. In addition, keratinocytes are also important players in the sensitisation phase, as they contain enzymes responsible for the conversion of pro-haptens into biologically active haptens, thereby facilitating their binding to endogenous proteins and making them make them immunogenic.

Although LCs can act as APCs, they are not required during the phase in which ACD is activated. In mice deprived of epidermal LCs by treatment with topical corticosteroids or UVB irradiation, the cutaneous hypersensitivity response is paradoxically higher than in control animals, suggesting that LCs are dispensable during the trigger phase and may be involved in the regulation of ACD [9].

Other cell types that may act as APCs are mast cells, infiltrating macrophages and keratinocytes [1••]. Keratinocytes, which constitutively express the MHC class I, have also been shown to inducibly express MHC class II and display APC-like properties in response to antigen exposure. In the absence of professional APC, MHC class II-bearing keratinocytes can, instead of triggering T-cell activation, induce hapten-specific clonal Th1 lymphocyte anergy, a type of T-cell tolerance that may play a role in limiting the extent and duration of ACD.

The hapten-triggered innate immune response results in the release of pro-inflammatory mediators. Among them, IL-1β, TNF-a and IL-18 are released from activated keratinocytes and LCs. Keratinocytes also secrete chemokines that attract T cells (e.g. CXCL9/10, CCL17, CCL20 and CCL27). T cells have to extravasate from the dermal blood vessels to reach the allergen-modified keratinocytes. Although antigen-specific migration of T cells may occur, most T cells are not recruited in an antigen-specific manner but are attracted to the skin by the expression of chemokines and adhesion molecules by keratinocytes, DC, fibroblasts, mast cells and endothelial cells [1••, 12]. Activated T cells present the homing antigen CLA, very late antigen (VLA)-4 and chemokine receptors. CLA binds to E-selectin, which is expressed on stimulated endothelial cells, and VLA-4 binds to the endothelial integrin vascular cell adhesion protein (VCAM)-1, which initiates diapedesis [13]. When they encounter their specific antigen, specific T cells proliferate in loco, which is

induced by mature DCs in combination with the antigen. Both CD4+ and CD8+ mediate the skin inflammatory response, but CD8+, which enter the skin first, tend to be the main effector cells [13]. The role of hapten-specific CD4+ T cells is not fully understood. CD4+ T cells appear at the site of challenge at a later time than CD8+ T cells and may play a different role in the inflammatory process [14]. CD4+ Th1 cells, which produce high levels of IFN-gamma and TNF-alpha, show cytotoxic activity against keratinocytes expressing MHC class II molecules and may cooperate with CD8+ T cells in enhancing the inflammatory response. In contrast, other subsets of CD4+ T-cells may have a regulatory function (e.g. FoxP3+ and CD4+ T-regulatory cells).

Following hapten exposure, natural killer T cells are stimulated and produce IL-4, leading to activation of type 1 B lymphocytes (B1) and production of specific IgM that cleaves complement to C5a, which then promotes the release of vasoactive substances such as serotonin and TNF-a by mast cells and platelets. [12]. In addition, C5a also functions as a chemoattractant for T cells and macrophages [15]. Th1 cells carrying the receptors CXCR3 or CCR5 are normally attracted to CXCL10 and CXCL9 along with CCL2 and CCL5, respectively. On the other hand, CCL20 and CCL27/CTACK (cutaneous T-cell attracting chemokine) preferentially attract CCR6+ and CCR10+ T cells, including Th1 and especially Th17 and Th22. CCL17/TARC (thymus and activation-regulated chemokine) preferentially attracts Th2 cells rich in CCR4. IL-8/CXCL8, produced in response to IL-17 and IL-22, attracts more neutrophils. The relative predominance of these distinct effector T can explain the clinical and histological variations in ACD reactions.

The infiltrated lymphocytes produce inflammatory cytokines such as INF-γ, IL-4, IL-17 and TNF-α. In response to INF-γ, keratinocytes upregulate adhesion molecules and cytokines/chemokines, which in turn stimulate the recruitment of even more T cells, NK cells, macrophages, mast cells and/or eosinophils to the targeted site [11••]. In the early phase of ACD, tissue damage is mainly due to apoptosis of keratinocytes carrying the hapten protein complex on MHC class I molecules, triggered by CD8+ T cells, via the perforin/granzyme or Fas/FasL pathways. IL-17 makes keratinocytes particularly sensitive to T-cell killing by Th1 cells. The initiation of keratinocyte apoptosis is accompanied by rapid cleavage of the intercellular CH1 adhesion molecules (E-cadherins). The loss of intercellular adhesion and the infiltration of lymphocytes into the epidermis are responsible for the intercellular oedema and vesiculation, as well as the typical spongiotic appearance of the epidermis in ACD [16]. This inflammatory response to eliminate antigen-modified keratinocytes results in loss of cell cohesion, destruction and desquamation. Also epidermal desquamation contributes to the removal of antigen and, gradually, the inflammatory process decreases [17]. The inflammatory response lasts for several days and then subsides after activation of downregulatory mechanisms (Fig. 1).

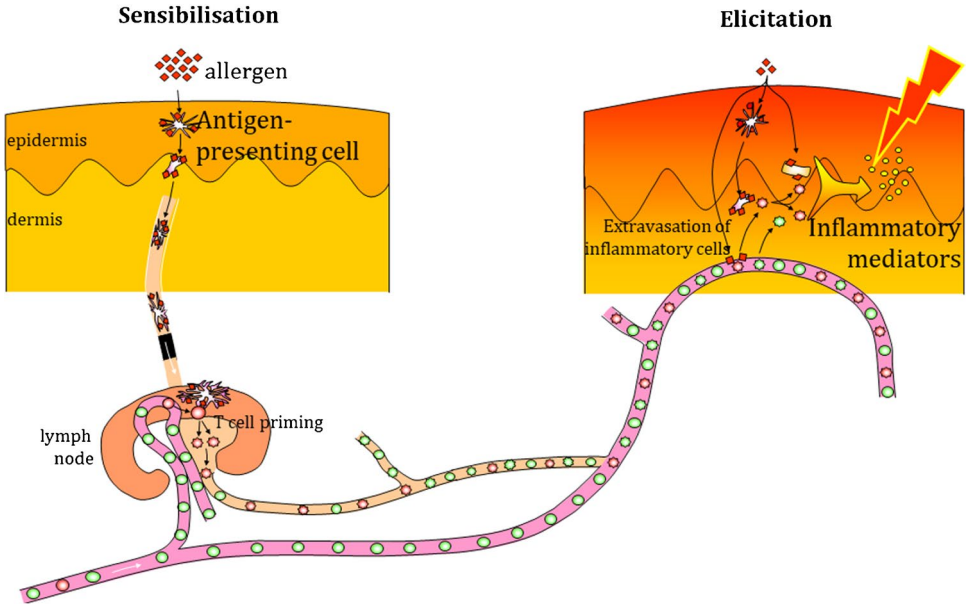

Fig. 1 Overview of the key elements in Allergic Contact Dermatitis

Regulatory mechanisms

Regulatory T cells (Tregs) may play a role in the sensitisation and elicitation phases of ACD. Also in the down-regulation of the inflammatory response, which was originally attributed to the removal of allergen from the skin [1••]. Tregs are a heterogeneous cell population that includes inducible Tregs (Tr1 and Th3 cells) and natural Tregs (CD4+CD25+Foxp3+ cells) [1••]. The skin contains mainly inducible Tregs that can be activated by LCs or dermal DC. After exposure to a contact allergen, Tregs can reduce or suppress the process of sensitisation. During the elicitation phase, they can suppress effector T cells in lymph nodes and inhibit leukocyte influx via IL-10 or CD39 mechanisms. Tregs may also be involved in the control and eventual termination of the inflammatory response in ACD [18].

Declarations

Conflict of interest
Thomas Rustemeyer declares that he has no conflict of interest.

Human and animal rights and informed consent
This article does not contain any studies with human or animal subjects.

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Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

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