4 Mechanisms in Allergic Contact Dermatitis

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4.1 Introduction

The skin is challenged everyday with an enormous variety of pathogens, as well as physical and chemical stimuli. In most cases, the skin immune system guarantees an efficient and protective response against hazardous stimuli, while preventing undesired responses towards innocuous substances. However, under certain conditions, undesired immune responses towards otherwise innocuous substances may occur. Allergic Contact Dermatitis (ACD) is the consequence of a deleterious immune reaction, mostly mediated by T lymphocytes, to small molecular weight chemicals-the haptens- that penetrate the skin and act as "danger signals", thus activating the innate immune system [1–3]. The sensitization phase of ACD results in the expansion of skin-homing hapten-specific T cells that, upon subsequent hapten challenge, migrate into the skin and induce the skin damage through the release of proinflammatory cytokines and by killing hapten-loaded keratinocytes.

Most of our knowledge on ACD derived from studies in murine models, the so-called contact hypersensitivity (CHS). In particular, those studies have elucidated the role of the diverse T cell subsets in the expression of the disease and have clearly demonstrated that contact sensitization is a highly regulated phenomenon, resulting from a delicate balance between the expansion of effector and regulatory T lymphocytes.

4.2 Chemical Nature of Skin Sensitizers

Most contact sensitizers are small (less than 500KD), chemically reactive, hydrophobic substances that have the capacity to penetrate the epidermal barrier, to diffuse into the extracellular compartment and, finally, to bind covalently to nucleophilic residues, usually ε-amino group of lysine or the thiol (SH) group of cysteine, of self-proteins [4]. Indeed, protein reactivity is mandatory for hapten recognition by the immune system since it allows the hapten to be presented in an MHC class I and class II-restricted manner to CD8+ and CD4+ T cells, respectively [5, 6]. A number of allergens, named pro-haptens, have minimal (or absent) chemical reactivity and their sensitizing potential is acquired upon in situ enzymatic activation [7, 8]. In most cases, pro-hapten activation consists in oxidative processes mediated by the

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cytochrome P450, although other enzymatic pathways, such as alcohol dehydrogenases, aldehyde dehydrogenases, monoamine oxidases have been also involved. It has been argued that the nomenclature should be extended by addition of a new term, namely 'pre-haptens', when the chemicals are not enzymatically activated, but converted abiotically by ambient or air oxidation to form hydroperoxides [9]. Exceptions to the general rule that state the requirement of a stable interaction between the hapten and the protein are metal salt, such as nickel, which interact non covalently with protein, in particular to histidine residues [10].

4.3 Haptens Act as Danger Signals and Activate the Innate Immune System

The potency of a skin sensitizer is determined not only by its chemical reactivity to proteins, but also by its intrinsic capacity to trigger the innate immune system. Recent data have provided evidence that haptens could directly or indirectly trigger pattern recognition receptors (PRRs), such as the Toll like receptors (TLRs) or the Nucleotide-binding oligomerization domains-like (NODS-like) receptors. TLRs are a family of at least 10 members (TLR1-10) of evolutionarily conserved receptors that recognize pathogen-associated molecular patterns (PAMPs) expressed by pathogens, and damaged-associated molecular pattern (DAMPs), released by damaged cells [11]. Main function of PRRs is to recognize "danger signals" at peripheral sites providing a rapid response aimed at preserving tissue homeostasis. Triggering of TLRs initiates a cascade of events that involve the activation of NFkB, IRF3/7 and inflammasome thus culminating with the secretion of the pro-inflammatory cytokines IL-1α, IL-1β, TNF-α, IL-6, IL-18 and type I interferons [12].

Nickel and Cobalt directly triggers TLR4, whereas other haptens could generate danger signals by inducing endogenous ligands for PRRs or promoting the production of ROS. For example, in murine models it has been demonstrated that the haptens 2,4,6 trinitrochlorobenzene (TNCB) and oxazolone indirectly activates PRRs by inducing hyaluronic acid breakdowns that function as TLR2 and TLR4 ligands [13]. An additional stimulus for the activation of the skin innate Immune system is the release of RNA, a ligand for TLR3, or ATP, a ligand for NLRP3 inflammasome, both released by damaged cells [14].

The importance of signals that activate the innate immune system in the sensitization process has been confirmed by studies demonstrating that the risk to develop an ACD to weak sensitizers is increased by the co-exposure to irritants or pathogens, that trigger the PRRs [15].

Activation of the skin innate immune system by haptens culminates in the secretion of a vast array of cytokines and chemokines. Keratinocytes are a critical source of pro-inflammatory mediators released during the early phase of skin sensitization, including IL-1α, IL-1β, IL-6, IL-18, TNF-α that affect other skin resident cells such as Langerhans cells (LC), dermal dendritic cells (DC), mast cells and endothelial cells. The role of mast cells in contact sensitization has been studied in murine models of CHS with contrasting results, being described either as required for the expression of the allergic reaction or rather being involved in the negative regulation of the inflammatory response [16, 17].

4.4 Role of Dendritic Cells in the Sensitization Phase of ACD

The cascade of signals induced by haptens results in the release of cytokines that induce the maturation and migration of skin-resident DC to regional lymph nodes. LC, the principal DC residing in the epidermis, make up 3–5% of all nucleated cells in the epidermis and are located near the dermal–epidermal junction, to form a network designed to "catch" foreign antigens that have entered the skin, including chemical allergens [18]. In steady state, the dermis hosts

at least 3 different subsets of DC that could be distinguished on the basis of the expression of the surface makers CD14, CD1a and CD141. The main role of DC is to link innate to adaptive immunity: DC collect danger signals at peripheral sites, process them in order to be recognized by the adaptive immune system, transport the signal to regional lymph node and finally instruct T and B cells to react appropriately to the specific antigen [19]. Immature DC residing in the skin are highly efficient in picking up antigens from the extracellular space and in processing them in endocytic compartments. Processing of hapten-protein complexes generates hapten-peptides that can be mounted on MHC class II and class I molecules for T cell recognition. Alternatively, hapten-epitopes could be generated in a processing independent manner, when the hapten bind directly to self-peptides contained in the groove of MHC molecules exposed on the membrane of DC. In parallel, under the effects of IL-1, IL-18 and TNF-α, DC undergo a maturation process and leave the skin to reach the regional lymph nodes. Maturing DC increase the expression of molecules involved in antigen presentation, such as MHC class I and class II and the co-stimulatory molecules CD80 and CD86, while decreasing progressively the endocytic capacity. Maturation also induces the expression of the chemokine receptor CCR7, that guide maturing DC to lymph nodes. In the last few years, the relative contribution of LC versus dermal DC in ACD has been largely debated. In a transgenic mouse model, selective depletion of LC, but not dermal DCs, resulted in an increased expression of CHS, thus indicating that the major DC population involved in the sensitization process are the dermal DC, and suggesting that skin LC may have a negative regulatory role [20]. Overall, these data have not been confirmed by other studies, indicating that the experimental setting, the strength of the sensitizer and the dose administered may be critical for the selective or combined intervention of the different subpopulation of DC during skin sensitization [21].

4.5 T Cells and the Effector Mechanisms of ACD

Efficient T cell presentation of hapten-epitopes by DC migrated in the paracortical area of regional lymph nodes determines the expansion of a variety of hapten-specific CD4+ and CD8+ T lymphocytes. The cytokine profile of hapten-specific T cells varies depending on the type of sensitizer, the strength of the co-stimulatory signals provided by the DC and by the cytokine milieu at the site of T cell priming. Generally speaking, most of the CD8+ T cells generated during the sensitization process belong to the Tc1 subset: upon stimulation they release abundant IFN-γ and TNF-α and possess prominent cytotoxic capacity thanks to the high expression of perforin and granzyme. Both in murine CHS and in human ACD, it has been demonstrated that the expansion of hapten-specific CD8+ T lymphocyte and their recruitment at the site of hapten challenge is mandatory for the development of the allergic reaction [22–26]. In contrast, CD4+ T cells expanded during ACD are more variegate in terms of cytokine production and function. Together with Th1, releasing IFN-γ and TNF-α, and Th2, releasing IL-4 and IL-13, a number of Th17 cells, releasing IL-17, and Th22 lymphocytes, releasing IL-22, can be isolated from the blood and, at higher percentage, from the skin of ACD patients [24]. Moreover, cells with a mixed Th1/Th17 phenotype could be isolated from skin lesion of ACD. These cells, thanks to the simultaneous release of IFN-γ, TNF-α and IL-17, display strong pro-inflammatory properties. Finally, DC-T cell encounter generate a variable number of CD4+ T lymphocytes with regulatory function. Hapten-specific T regulatory cells 1 (Tr1) release abundant IL-10 upon activation and limit the magnitude of the immune response, whereas CD25+ Foxp3+ T cells are critical for the maintenance of immune tolerance not only versus self-antigens but are also involved in the peripheral tolerance versus potential sensitizers.

DC not only determine the functional properties and the cytokine repertoire of T lymphocytes,

but they also induce on differentiating T cells a specific repertoire of chemokine and homing receptors that confer the capacity to circulate preferentially in the cutaneous environment. Skin homing T cells display the cutaneous lymphocyte associated antigen (CLA) that binds e-selectin expressed on activated skin microvasculature. Independently from their cytokine profile, skin-homing T cells also express the chemokine receptor CCR4, that serve as a ligand for CCL17 and CCL22, abundantly expressed in inflamed skin [27].

Re-exposure to the relevant hapten in sensitized individuals, activates the skin innate immune system and determines the release of a multitude of pro-inflammatory cytokines. IL-1 and TNF-α promote the synthesis and expression of selectins, adhesion molecules and membrane-bound chemokines on endothelial cells. The augmented adhesiveness of skin microvasculature determines the rapid recruitment of circulating leukocytes at the site of hapten challenge.

Although DC are required for efficient priming of hapten-specific naive T cells in the sensitization phase of ACD, they are not required for the activation of memory/effector T lymphocytes migrating in the skin during the efferent phase of the allergic reaction. In this scenario, also non-professional antigen presenting cells, such as macrophages and endothelial cells can efficiently activate T lymphocytes and initiate the inflammatory reaction leading to the clinical manifestation of ACD.

The eczematous reaction is the consequence of two main mechanisms: (i) induction of keratinocyte apoptosis, mostly mediated by hapten-specific CD8+ T cells, and (ii) release of proinflammatory cytokines by infiltrating CD4+ lymphocytes and NK cells. Although CD4+ T cells in ACD skin outnumber CD8+ lymphocytes, the latter are crucial for disease expression. The relative contribution of CD4+ and CD8+ T lymphocytes in the expression of inflammatory responses to skin sensitizers have been originally demonstrated in the murine model of CHS, using MHC class II and MHC class I KO mice. In this experimental setting, MHC class II deficient mice, that are depleted of CD4+ T cells, showed a much-increased ear thickness upon hapten challenge compared to littermate controls, whereas in MHC class I deficient mice, that are depleted of CD8+ T cells, inflammation was strongly reduced [28]. Furthermore, transgenic mice lacking Fas ligand (FasL) and perforin genes, both involved in T cell-mediated cytotoxicity, fail to mount CH reactions, thus demonstrating that cytotoxic mechanisms against keratinocytes are mandatory for full expression of murine CHS [28]. The role of CD8+ T cells have been afterword indirectly confirmed in human beings, by demonstrating that nickel-allergic but not non-allergic individuals, bear circulating nickel-specific CD8+T cells responsible for induction of keratinocyte apoptosis in the early phase of ACD [24, 29, 30].

Keratinocyte apoptosis determines the cleavage of E-cadherins, adhesion molecules involved in keratinocyte homotypic adhesion, thus leading to epidermal spongiosis [31]. $CD4^+$ lymphocytes play a dual role in ACD. Activated $CD4^+$ Th1 lymphocytes secrete IFN-γ and TNF-α, which are critical for the engagement of keratinocytes and other skin-resident cells in the inflammatory process. In particular, type 1 cytokines promote the expression of MHC class II and ICAM-1 molecules and the secretion of a plethora of cytokines and chemokines in keratinocytes, such as CXCL1, CXCL8, CXCL10, CCL1, CCL5, CCL20, CCL22, that contribute significantly to the recruitment of new waves of leukocytes at the site of hapten exposure. IL-17, released by Th17 and by Th1/17 cells, synergize with TNF-α and IFN-γ in the induction of ICAM-1, thus promoting the interaction between keratinocytes and T cells, and in the production of CXCL8 by keratinocytes. Finally, Th1 cells could contribute to the induction of apoptosis of keratinocyte at a later time point, when keratinocytes exposed to IFN-γ, become MHC class II+ and can present hapten epitopes to CD4+ T lymphocytes. Th1-mediated, in contrast to CD8+ T cells-mediated, cytotoxicity is mostly dependent on the Fas-FasL pathway [30].

Despite the general assumption that ACD is a Th1/Th17-mediated reaction, more recently it has been demonstrated that the T cells involved in the allergic reaction could have distinct cytokine profiles depending on the chemical characteristic of the hapten.

Indeed, studies investigating the gene expression in ACD patients identified a significant number of genes that were regulated in a contact allergen-specific manner. For example, ACD to nickel showed a potent induction of innate immunity-related genes and a predominant Th1/Th17 and a Th22 response; in contrast, fragrances ACD, evidenced a strong expression of Th2 cytokines with a limited Th1/Th17 contribution [32].

Also, neuroendocrine factors have a key role in T-cell differentiation [33–36]. An important link has been established between nutritional deprivation and decreased T-cell-mediated ACD reactions [37]. For example, leptin, that is released by nourished and functioning fat cells, is required for type-1 T-cell differentiation [36]. Moreover, androgens, estrogens and adrenal cortex-derived steroidhormones promote Th1 cell polarization, IFN-γ production while suppressing IL-4 release [38, 39]. In contrast, the female sex hormone progesterone favors the development of Th2 cells [40].

NK cells constitute the 5-10% of the cellular infiltrate in ACD skin. Most of the skin-infiltrating NK cells display a CD3-CD56+ CD16- phenotype and release IFN-γ and TNF-α upon exposure to activating signals, such as the cytokines IL-2 and IL-15. ACD-infiltrating NK cells can contribute to the tissue damage not only by releasing type 1 cytokines in the skin microenviroment, but also because once activated they can induce keratinocyte apoptosis in a perforin/granzyme-dependent manner [41]. In murine CHS, evidence has been provided that NK cells specific to hapten epitopes are expanded upon exposure to the sensitizer [42]. Such a finding has not been confirmed in human beings, so far (Fig. 4.1).

4.6 Regulation of ACD

The regulation of immune responses to environmental antigens is a critical task for the skin immune system, that involves multiple

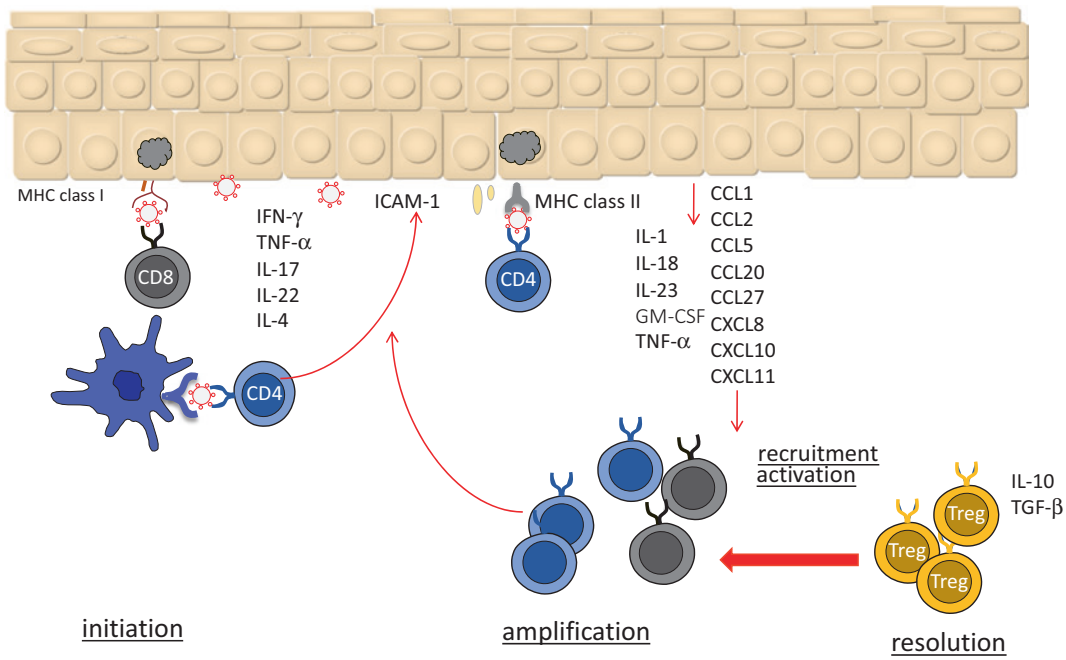

Fig. 4.1 Effector and regulatory mechanisms in allergic contact dermatitis

mechanisms, including apoptosis of effector T lymphocytes due to activation induced cell death, induction of T cell anergy, release of anti-inflammatory cytokines, and expansion of specialized subsets of T lymphocytes with regulatory function (Treg).

Most of our knowledge about the tolerogenic mechanisms in skin hypersensitivity to chemicals derives from murine models of CHS. At least two tolerogenic models have been widely investigated: haptens painted upon UVB-irradiated skin induces a specific immune tolerance that can be transferred with lymphocytes to naïve animals. UVB-induced immune tolerance appears dependent upon the expansion of IL-10+ CD4+ CD25+ T reg cells [43, 44]. The second model, named oral tolerance, consists in oral feeding the animal with the skin sensitizer. In such a case, the hapten activates the gut immune system and determines the expansion of TGF-β+ T cells and IL-10+ T cells with regulatory function that prevent the occurrence of skin hypersensitivity upon re-exposure to the sensitizer [45]. It has been shown that oral tolerance depends on TLR4 expression on hematopoietic cells, being necessary for the mobilization of tolerogenic CD103+ CD11c+ lamina propria DC to the local lymph nodes and to induce the expansion of Foxp3+ Tregs [46].

Treg cells are an heterogenous family of T lymphocytes that display immune-suppressive function with various mechanisms. T regulatory cells 1 (Tr1) have been described both in mice and in humans, as in vitro slow-proliferating cells that release IL-10, but not IFN-γ, IL-4 or IL-17 upon activation, and are believed to be central regulators of the extent and duration of ACD responses. to regulate immune responses to haptens in vitro [47, 48]. A second population of regulatory cells, the $CD4^+CD25^+$ Foxp3+ Treg lymphocytes, have been first identified in mice as a distinct T cell lineage that originate in the thymus and guarantee the peripheral tolerance to self-antigens. Evidence have been provided that a similar T cell lineage, the induced or adaptive $CD4^+CD25^+$ Foxp3+ Treg, are expanded in secondary lymphoid organs following the encounter with environmental antigens, including chemicals [49] The role of $CD4^+CD25^+$ Foxp3+ Treg in regulating T cell responses to skin applied haptens have been demonstrated both in murine CHS and in human ACD to nickel [50]. Mechanisms involved in the CD25+ Treg-mediated immune suppression are multiple and include the release of regulatory cytokines, such as IL-10 and TGF-β, the expression of CTLA-4, which bind CD80 and CD86 on DCs and induces the production of indoleamine 2,3-dioxygenase (IDO).

Finally, in mice, evidence has been provided of the existence of B cells with regulatory function. Breg cells modulate CHS expression by two mechanisms: the secretion of IL-10 and by inducing apoptosis in activated T cells through a Fas-FasL mechanism [51]. Interestingly, CD1d-deficient mice show increased CHS responses, paralleled by a reduction of IL-10+ Bregs in secondary lymphoid organs, suggesting a critical regulatory role of NKT cells in skin hypersensitivity [52].

4.7 Conclusions

New insights into ACD mechanisms have been possible thanks to the availability of animal models and in vitro techniques, which allowed a precise identification of inflammatory pathways governing the immune reaction.

In the future, the big challenge will be the identification of biomarker with prognostic value, especially in prediction occupational ACD, and the characterization of markers that support the differential diagnosis between ACD, irritant contact dermatitis and other inflammatory skin diseases. In this scenario, recent promising studies have been conducted with preliminary results, that will require further investigation to be confirmed [53–56].

Finally, the management of ACD could benefit from studies focused on the induction of tolerogenic signals that could dampen the allergic reaction to environmental substances. The recent reports indicating that some cell-wall proteins of commensal bacteria act as ‘safety’ signals that actively antagonize TLR4 signaling

and induce immunologic tolerance [57, 58] may represent a potential and innovative therapeutic approach.

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