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REVIEW

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Intricate Relationship Between Adaptive and Innate Immune System in Allergic Contact Dermatitis

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Allergic contact dermatitis (ACD) is a complex immunological allergic disease characterized by the interplay between the innate and adaptive immune system. Initially, the role of the innate immune system was believed to be confined to the initial sensitization phase, while adaptive immune reactions were linked with the advanced elicitation phase. However, recent data predicted a comparatively mixed and interdependent role of both immune systems throughout the disease progression. Therefore, the actual mechanisms of disease progression are more complex and interlinked. The aim of this review is to combine such findings that enhanced our understanding of the pathomechanisms of ACD. Here, we focused on the main cell types from both immune domains, which are involved in ACD, such as $CD4^+$ and $CD8^+$ T cells, B cells, neutrophils, and innate lymphoid cells (ILCs). Such insights can be useful for devising future therapeutic interventions for ACD.

INTRODUCTION

Allergic contact dermatitis (ACD) is an inflammatory skin disease, affecting around 15% of the population worldwide [1]. In Europe, 40% of occupational health problems are related to the skin and 90% of them account for contact dermatitis [2]. Recent data showed that almost 27% of European adults are sensitized to at least one contact allergen and they are on the verge of developing ACD [3]. Clinically, pruritus, vesicles, erythema, and dry scaly patches on the skin characterize the disease. The most commonly affected parts of the body are hands, arms, and

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Abbreviations: ACD, allergic contact dermatitis; ILCs, innate lymphoid cells; DCs, dendritic cells; APC, antigen-presenting cells; DTH, delayed type hypersensitivity; dLN, skin-draining lymph nodes; Bregs, regulatory B cells; Treg, regulatory T cells.

Keywords: Allergic contact dermatitis, Lymphocytes, Innate immune cells, Adaptive immune cells.

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face [4-6]. The symptoms of the disease affect the quality of life and put a strong socio-economic impact of approximately 1 billion dollar annual loss in the US alone [7]. Therefore, there is a strong need of (pre)clinical research to better understand the immunological mechanisms of ACD and to find out effective treatment strategies. In this article, we focus on the recent advancements made by the interconnecting role of innate and adaptive immune cells in ACD. We encompass our current understandings about the pathomechanisms of ACD that would be helpful for planning future therapeutics.

PATHOPHYSIOLOGY OF THE DISEASE

ACD is a common skin disease evoked by delayed type hypersensitivity (DTH) responses to low molecular weight chemicals and metal allergens. The disease pathology is comprised of two distinct phases; the initial sensitization and subsequently, the elicitation phase. The sensitization phase starts when the susceptible individuals encounter skin contact with the allergen for the first time. Allergens are small molecular weight molecules such as urushiol, poison ivy, fragrance mixes, wool alcohol, rubber mixes, methylisothiazolinone, or metal ions such as nickel, chromium, cobalt, and gold [8-11]. These low molecular weight allergens are incomplete antigens (so-called haptens). After passing through the skin barrier they bind to cellular proteins to become immunogenic by triggering T cell responses [12-14]. Two distinct subsets of dendritic cells (DCs) are involved in allergen uptake and subsequent presentation to T cells. Tissue-resident langerin$^+$ epidermal DCs, known as Langerhans cells (LCs) reside in the epidermis while langerin$^-$ dermal dendritic cells (DDCs) patrol in the dermis [15,16]. After taking up hapten-protein complexes they migrate to skin-draining lymph nodes (dLN) where they act as antigen-presenting cells (APCs) (Figure 1). In dLN, the APCs prime naïve CD4$^+$ and CD8$^+$ T cells by presenting the antigen in the context of MHC (I or II) cell surface molecules. This exposure triggers the differentiation and proliferation of CD8$^+$ and CD4$^+$ T cells into IFNγ producing cytotoxic T cells (Tc) and helper T (Th) cells, respectively [17,18].

Those T cells then reside in the dLN as effector memory cells until the next exposure of the same allergen. The elicitation phase of ACD is the clinically obvious phase in which inflammatory signs become visible in the patient. In case of allergen re-exposure in a sensitized individual, effector memory cells proliferate and subsequently migrate from dLN to the site of allergen contact. This activation and migration of T cells is mediated by the allergen-induced production of chemokines and cytokines from native DDCs, LCs, and keratinocytes [19-22]. The recruitment of activated T cells results in epidermal tissue destruction, such as vesicle and blister formation, erythema, itch, and other inflammatory signs [23]. Recently, such acute responses have been attributed to skin tissue-resident memory T (Trm) cells. Trm cells induce acute allergic responses as fast as 24 hours after allergen exposure [24]. The effector T cells of ACD mainly produce inflammatory cytokines including interferon (IFN)-γ, interleukin (IL)-1α, IL-6, IL-17, IL-26, Tumor necrosis factor (TNF)-α, and IL-23 at the site of inflammation and promote further recruitment of cytotoxic T cells and innate immune cells to enhance the allergic responses [25-28]. At the same time, the regulatory arm of adaptive immune system, namely Foxp3$^+$ IL-10$^+$ regulatory T cells (Tregs) and IL10+ regulatory B cells (Bregs) downregulate the inflammatory responses of cytotoxic T cells and innate immune cells [29,30]. In this review we have discussed the role of all these important cells that mediate the disease initiation, progression, maintenance, and suppression.

ROLE OF ADAPTIVE IMMUNITY IN ACD

Adaptive immune responses in ACD start with the sensitization phase when hapten bearing APCs migrate from skin to local lymph nodes and present the antigens to naïve T cells [31]. This antigen presentation through MHCI or MHCII molecules activates naïve CD8$^+$ or CD4$^+$ T cells, respectively [32]. It leads to priming and clonal expansion of antigen-specific T cells and later on to their migration to the skin upon the second antigen exposure resulting in DTH reaction. DTH is a T cell-mediated inflammatory response evolving 24 to 48 hours after allergen exposure [33]. The "classical cells" of DTH are CD4$^+$ T cells, but in case of ACD the major T cell effector functions are attributed to CD8$^+$ T cells. This was demonstrated by monoclonal antibody (mAb)-dependent depletion of CD4$^+$ or CD8$^+$ T cells *in vivo* in the contact hypersensitivity (CHS) mouse model of ACD. The depletion of CD8$^+$ cells showed a marked reduction in the CHS reactions while depletion of CD4$^+$ cells resulted in a strong enhancement of CHS [34]. In another CHS study, mice with an inactivated MHC I gene within the CD8 compartment (leading to a drastic decrease in CD8+ T cells) showed a diminished allergic response to 1-Fluoro-2,4-dinitrobenzene (DNFB), one of the classical obligatory contact-sensitizing haptens used to evoke CHS. On the other hand, MHC II knock-out mice lacking CD4$^+$ T cells showed a fulminant allergic response [35].

Crosstalk between CD4$^+$ and CD8$^+$ T cells in ACD

There are numerous studies which indicate an important role of different CD8$^+$ cytotoxic T cells (IFNγ secreting Tc1 while IL4 and IL5 secretingTc2 cells) in ACD. In addition, keratinocytes also play a significant

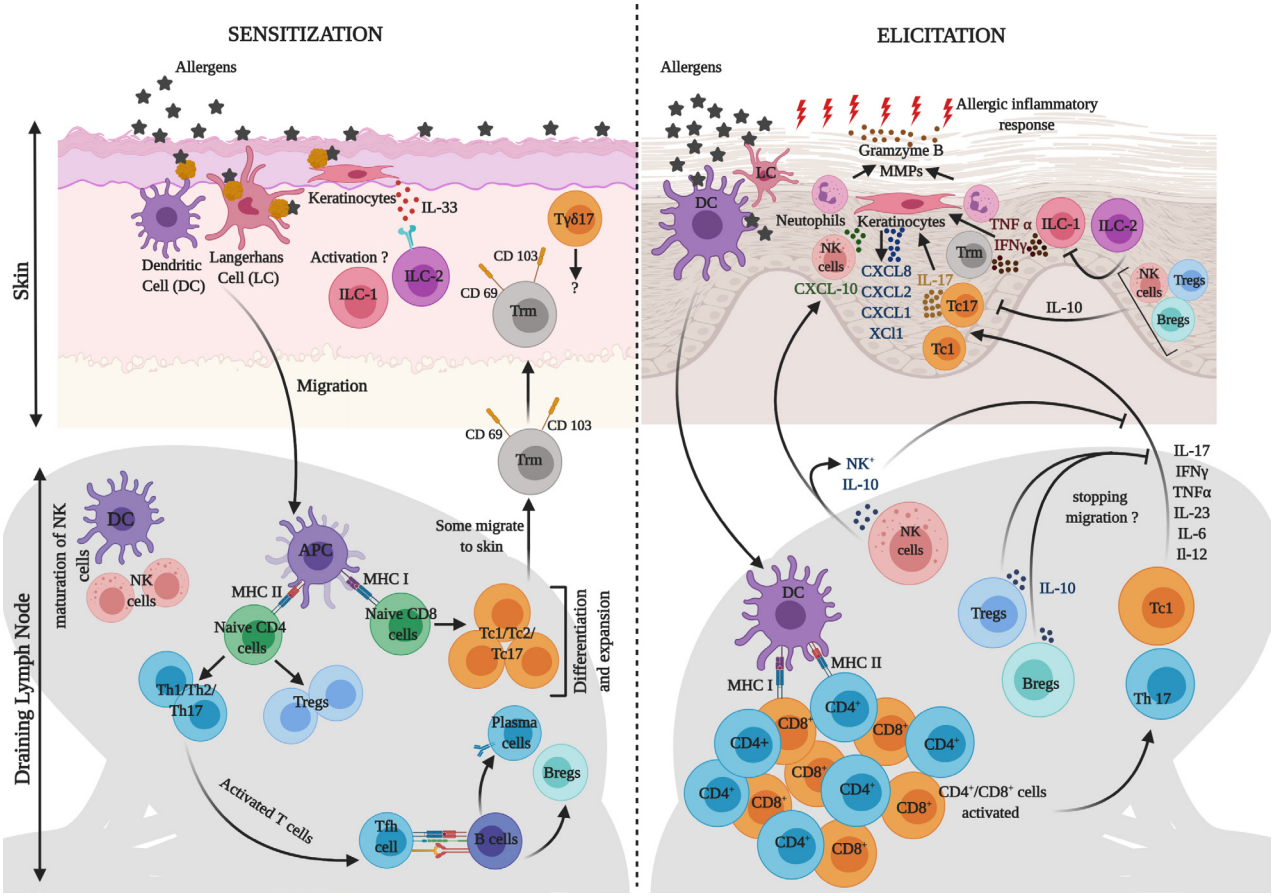

Figure 1. Pathophysiology of allergic contact dermatitis (ACD) showing the immunological response during the sensitization and elicitation phases.

role by secreting chemokines and cytokines in response to allergen application. In the early stages of the elicitation phase, these chemokines attract Tc1 and Tc2 cells towards the skin where they induce tissue damage and acute inflammatory signs [36]. In the later stage, IFNγ and TNFα prime keratinocytes for expression of ICAM-I and MHC II molecules, leading to the recruitment of $CD4^+$ Th1 cells. The recruitment of $CD8^+$ Tc1 and Tc2 cells is largely independent of IFNγ [37]. Therefore, one may speculate that $CD8^+$ T cells induce early cytotoxicity and edematous inflammation, while $CD4^+$ T cells act later by inducing more modulatory effects.

The inflammatory effects of $CD8^+$ and $CD4^+$ are dependent on a library of different cytokines. It includes IL-1α, IL-6, IL-12, IL-17, IL-22, IL-23, TNFα, TGFβ, and IFNγ, secreted by lymphocytes, APCs, and epithelial cells (*e.g.* keratinocytes) [38,39]. IL-1α is part of the IL-1 family of cytokines which includes 11 pro-inflammatory and anti-inflammatory cytokines [40]. IL-1α and IL-1β are pro-inflammatory cytokines and both bind to the IL-1 receptor (IL-1R). Their activity is modulated by an intrinsic IL-1R antagonist (IL-1Ra). Other members of the family include three isoforms of IL-36 which bind to its respective receptor (IL-36R) and are responsible for inflammatory responses. Alike IL-1, IL36 mode of action can be blocked by IL-36Ra. IL-18 and IL-33 are also part of the IL-1 family and produce inflammatory responses by binding to IL-18Rα and interleukin-1 receptor-like 1(ST2) receptor respectively [41]. The disturbed balance between pro- and anti-inflammatory IL-1 family cytokines is linked to the development of ACD. Mattii *et al.* have reported an increase in IL-1β, IL-36, and IL-33 in skin biopsies from ACD patients [42].

In the context of ACD, IL-17 is a signature cytokine and therefore is a major player for inducing inflammatory symptoms [43,44]. Both $CD4^+$ and $CD8^+$ T cells known as Th17 and Tc17 respectively, can produce IL-17 [45] and a crosstalk between these cells play an important role in ACD. Murine Th17 polarization starts after naïve $CD4^+$ T cells have experienced antigen signals in the presence of IL-23, IL-1β, and IL-12. In addition, IL-6 inhibits the Treg pathway and allows TGFβ to act as a driver for Th17 polarization. After differentiation, Th17 cells secrete IL-21, IL-22, IL-17A, and TGFβ [46]. Similar polarizing conditions are required for the development of Tc17 cells with the dual capacity to secrete IL-17 and

IFNγ [47]. The role of IL-17 in ACD was first reported by detecting IL-17 mRNA in skin samples of nickel allergic patients [48]. Later on, *in vitro* studies showed that $CD4^+$ T cells are capable of producing IL-17 and IFNγ after stimulation with PMA and ionomycin [49]. In humans the role of Th17/Tc17 is linked to the elicitation phase of ACD. Zhao *et al.* showed a significant increase in Th17/Tc17 infiltration in human ACD skin biopsies along with marked expression of RORγt and other Th17/Tc17 specific cytokines (IL-17A, IL-17F, IL-21, and IL-22) [50]. Furthermore, *in vivo* evidence for a role of Th17 cells in CHS was presented by using IL-$17^{-/-}$ mice. These mice displayed a decreased ear inflammation after allergen exposure and ear swelling, surrogate marker of skin inflammation, was diminished by adoptive transfer of $CD4^+$ T cells from wild type mice [51]. On the other hand, the role of Tc17 cells in CHS/ACD has been underestimated as compared to Th17 cells. The effector function of Tc17 cells in CHS were first reported by *in vivo* depletion of $CD4^+$ and $CD8^+$ T cells before DNFB sensitization. Mice depleted of $CD8^+$ T cells showed reduced ear swelling, while $CD4^+$ depletion enhanced the inflammation [52]. For further confirmation, DNFB-primed $CD8^+$ T cells were adoptively transferred in Rag-$1^{-/-}$ mice. Upon elicitation, these mice exhibited a prominent CHS reaction that was inhibited by IL-17 neutralization. These findings suggest a context-dependent role of both cell types in CHS, depending on the mouse model and the nature of the allergen used. It is possible that $CD8^+$ T cells become dominant during CHS responses by inducing Fas-mediated apoptosis of $CD4^+$ T cells after allergen application. However, in the absence of $CD8^+$ T cells, $CD4^+$ T cells are fully capable of inducing hypersensitive response [53].

Besides IL-17, Th17/Tc-generated IL-26 is another cytokine involved in ACD. IL-26 is an important member of the IL-10 cytokine family and is predominantly produced by Th17, Th1, and NK cells [54,55]. Previously, it was known for its anti-microbial activity by recruitment of various innate immune cells and Th17 cells. More recently, however, IL-26 generated by Th17 cells was reported to be important for the development of ACD in humans [56] implying that IL-26 is not only important for antimicrobial activity but also inflammatory responses.

ROLE OF IL-17 IN ACD

There are six different types of IL-17 cytokines (IL17 A-F), produced as homo and heterodimers from $CD4^+$ T, $CD8^+$ T, γδT, natural killer (NK) cells, neutrophils, mast cells, and epithelial cells [44]. The most potent proinflammatory type is IL-17A, which exerts its functions by inducing various pro-inflammatory molecules and recruiting different types of cells [57]. It induces the production of granulocyte-colony stimulating factor (G-CSF) and granulocyte-macrophage CSF (GM-CSF), thereby attracting neutrophils and monocytes to the site of inflammation [58,59]. In addition to IL-6 and TNFα cytokines, IL17 also stimulates the production of various chemokines such as CXCL2, CXCL5, CXCL10, CCL20, and CCL2, which are responsible for the recruitment of monocytes and macrophages [60,61]. Notably, CCL20 binds to its receptor CCR6, which is preferentially expressed on Th17/Tc17 cells thereby supporting a positive skin inflammation feedback loop [62]. Moreover, IL-17 induces the production of matrix metalloproteinases (MMP1-3) in myeloid skin infiltrating cells resulting in tissue damage by extracellular matrix proteins [63]. In conclusion, IL-17 exerts its inflammatory role by bridging adaptive immune responses to the innate immune system and inducing tissue damage. Contrary to the tissue-damaging effect of IL-17, a recent finding also suggested its homeostatic role. In this study, mice deficient for neonatal $V\gamma2TCR^+$ Tγδ17 cells were used as an atopic dermatitis (AD) mouse model. The study showed that IL-17 controls AD development by maintaining balance in the population of αβT cells, skin commensal bacteria, and rate of basal keratinocyte differentiation [64]. This indicated that neonatal γδT cells behave like innate regulatory T cells in the skin. Such a homeostatic role of IL-17 needs further investigation in the context of ACD/CHS which would further enhance our understanding of the functionality of IL-17 during different inflammatory disorders.

Role of IL-10 in ACD

ACD is a self-limiting disease, once the contact allergen is removed, inflammatory symptoms begin to resolve. On the cellular level, the resolution is dependent on regulatory T (Tregs) and B (Bregs) cells [65,66]. Tregs cause suppression of activated T cells by expressing the anti-inflammatory cytokines IL-10 and TGFβ. They also induce cellular anergy through surface-bound molecules such as PD-1 and CTLA-4 [67-69]. In case of chronic ACD, activated $CD8^+$ T cells turn into tissue-resident memory T cells ($CD8^+$ Trm) which are capable of eliciting a fulminant immune response upon re-exposure to allergen [24,70]. It has been reported that the activity of these Trm cells is controlled by inhibitory checkpoint receptors such as CTLA-4, PD-1, and TIM-3 [71]. Removal of these checkpoint inhibitors facilitates the induction of recurrent allergic response even with low amount of allergen. Apart from anergic T cell markers, IL-10 acts as a major suppressive agent of Tregs in ACD. Other than B and T cells, IL-10 may be produced by numerous cell types including DCs, neutrophils, macrophages and NK cells [72]. IL-10 exerts its suppressive function by activation of STAT3. Activated STAT3 modifies the pro-inflammatory transcriptome directly or indirectly by inducing transcriptional or post transcriptional modifications

respectively [73]. On other hand, it also starts the transcription of suppressor of cytokine signaling 3 (SOCS3) and IL-1Ra. SOCS3 downregulates the TNFα production by inhibiting the activation of mitogen activated protein kinase (MAPK) and NF-κB-signaling pathways which lead to further reduce the expression of pro-inflammatory cytokines [74-76]. Therefore, IL-10 producing Tregs are in the focus of therapeutic approaches for ACD treatment. Despite the production of IL-10 from $CD8^+$ T cells, CD8 Tregs appeared to be dispensable for the resolution of CHS. Mice deficient for $CD8^+$ $IL\text{-}10^+$ T cells showed CHS responses comparable to wild-type controls. Even in the absence of $CD4^+$ T cells, IL-10 production from $CD8^+$ T cells could not resolve inflammation [77]. Therefore, it is implicated that in terms of ACD/CHS, IL10 producing $CD8^+$ T cells may play an effector role while regulatory $CD4^+$ T cells can exert a regulatory role in controlling allergic responses.

B CELLS IN ACD

B cells play crucial roles in protection against infectious diseases by contributing to the immune responses through antigen presentation, cytokine, and antibody production. In addition to antibody-secreting B cells, Bregs have been reported [78-80]. Through the action of IL10 Bregs exert immunosuppressive capacities to modulate or control various inflammatory diseases [79,81,82]. Several studies have revealed the significance of B cells in CHS/ACD [83,84]. B cell deficiency worsened the CHS responses, hence providing a protective role of B cells in allergic inflammatory diseases [66]. The ablation of the B cell-specific peroxisome proliferator-activated receptor γ (PPAR-γ), a member of the nuclear hormone receptor superfamily, impaired the regulatory function of B cells in a CHS mouse model. This resulted in enhanced CHS responses after 48 hours of challenge. It was observed that the expression of IL-10 was significantly decreased by $CD19^+$ B cells and $CD5^+$ $CD1d^{hi}$ cells in PPAR-γ-deficient mice, contributing to the reduced regulatory function of B cells. However, the development of B cells was unaffected by the loss of PPAR-γ [85]. It is suggested that the immunosuppressive effects of UVB irradiation in a CHS mouse model were attributed to the inhibition of T cell proliferation by Bregs. The Bregs were induced by UVB via Toll-Like receptor (TLR) 4 whereby the deficiency of TLR-4 not only impaired the inhibitory function of B cells but also reduced the therapeutic effects of UVB on CHS responses [86]. Further data on Bregs have shown that the presence of two distinct Bregs subsets, namely splenic $CD1d^{hi}$ $CD5^+$ B cells and peritoneal B1 cells, inhibit the CHS response. Of interest, splenic $CD1d^{hi}$ $CD5^+$ B cells suppress the acute phase of CHS whereas the less significant peritoneal B1a cells are believed to help in suppressing the late remission phase. However, the role of B1 cells in CHS remains yet controversial [66].

ROLE OF THE INNATE IMMUNE SYSTEM IN ACD

Traditionally, the role of the innate immune system is believed to be restricted to the sensitization phase of ACD, which is characterized by antigen presentation by DCs and early responses by macrophages, natural killer cells, and neutrophils. However, in recent studies the role of the innate immune system has found to be expanded till later stage of elicitation. Studies on metal allergy indicate that innate immune system play pivotal role in CHS responses [11,14,87]. Schmidt *et al.* have shown that Nickel ions interact with three histidine residues (H431/H456/H458) within the interaction domain of humanTLR-4 and trigger the formation of tetrameric complexes consisting of two TLR4 and two myeloid differentiation protein 2 (MD-2) co-receptor molecules. These complexes initiate a downstream signal cascade that lead to the activation of pro-inflammatory nuclear factor kB (NF-kB) transcription factors [88]. Here we want to focus on different innate immune cells as well as newly identified innate lymphoid cells (ILCs).

Neutrophils in ACD

Neutrophils are among the first recruited cells to the site of inflammation and their recruitment is dependent on C-X-C chemokines such as CXCL8, CXCL2, CXCL1, and CXCL5 [89]. Pathological function of neutrophils relies on the metalloproteinase and granzyme B dependent degradation of extra cellular matrix and attraction of macrophages to the site of inflammation [90]. More than two decades ago, Laan *et al.* showed that IL-17 plays an important role in neutrophil recruitment via C-X-C chemokine release [91,92]. Perturbation of neutrophil infiltration to the site of allergen exposure leads to reduced allergic responses. Leukotriene B4 is a potent chemo attractant for neutrophils in allergic diseases [93]. Epicutaneous application of 2,4,6 Trinitrochlorobenzene (TNCB) onto Leukotriene B4 $(Ltb4)r1^{-/-}$ deficient mice showed a decreased neutrophil infiltration to ear skin and reduced inflammation as compared to wild type mice [94]. Moreover, depletion of neutrophils showed that they are important for both stages of ACD. Their role in the sensitization and elicitation phases was determined by using $Mcl1^{\Delta Myelo}$ neutrophil-deficient mice and by anti-Ly6G dependent neutrophil depletion. Adoptive transfer of lymph node cells from wild type mice sensitized by TNCB showed that CHS responses cannot be recapitulated in $Mcl1^{\Delta Myelo}$ mice [95]. This indicates that neutrophils are actively involved in both phases of ACD. Moreover, it is proposed that neutrophils facilitate the

depletion of T cells and ILCs, suggesting a much more complex association between neutrophils and adaptive immune responses [96,97].

Innate Lymphoid Cells in ACD

Innate lymphoid cells (ILCs) belong to the lymphoid lineage and share a common origin with T, B, and NKT cells. During development, upregulation of transcription factor T cell factor 1 (Tcf-1) in common lymphoid progenitor (CLP) cells gives rise to early innate lymphoid progenitor (EILP) cells. From this stage, two developmental branches appear, one leads to $EOMES^+$ NK cells, and the other gives rise to three different types of ILCs (ILC 1-3) [98].

Natural killer cells: NK cells have recently been identified as an important cell type for ACD. They produce IFNγ and regarded as innate counterparts of $CD8^+$ T cells. Human $CD56^{high}$ $CD16^-$ $CD62L^-$ NK cells were characterized for the first time by Carbone *et al*. for their role in ACD. In mice, NK cells have two further subdivisions, $CD49a^-$ $DX5^+$ conventional NK (cNK) cells and $CD49a^+$ $DX5^-$ liver resident NK cells [99]. Mice NK cells also express CD62L and CCR7 for localizing to secondary lymphoid organs where they foster DC maturation and T cell priming [100]. $EOMES^+$ cNK cells are among the first responders in CHS after allergen exposure and evoke an acute inflammatory response within 24 hours of allergen application [101]. Their recruitment to skin is also facilitated by the CXCL10 chemokine as they express CXCR3, CCR5, and CCR6 chemokine receptors [102]. Besides cNK cells, another unique type of NK cells, with restricted repertoire of TCR αβ chains known as NKT cells, is involved in CHS responses [103]. NKT cells detect glycolipid antigens by CD1d (MHC analogue) bound on LCs, DCs, and keratinocytes [104,105], which is followed by production of IFNγ, TNFα, and the induction of apoptosis in affected cells [106]. Cytotoxicity of NKT cells can be controlled by inhibiting the CD1d mediated function of antigen presentation, which provides a potential window for therapeutic intervention of ACD [107].

NK cells alone can induce CHS responses independent of T and B cells. Ly49 $C\text{-}I^+$ NK cells can mediate an antigen-specific long lasting CHS reaction. Likewise, DNFB application can induce fulminant inflammatory responses in $Rag^{-/-}$ mice and localization of NK cells to inflamed skin. Moreover, transfer of NK cells from DNFB-sensitized $Rag2^{-/-}$ mice to naïve mice reproduced the CHS response, which indicates a capacity of NK cells for retaining hapten-specific memory [108]. Although NK cells constitute a minor population of skin infiltrating cells in CHS, they contribute massively to the development and regulation of CHS responses. Of interest, NK cells also produce IL-10, thereby suppressing $CD8^+$ T cell mediated ACD, independent of Tregs [109,110]. These findings suggest a broad and comprehensive role of NK cells in ACD and propose important intervention opportunities for therapeutic purposes.

Innate lymphoid cells (ILC1-3): Due to the expression of the transcription factor Tbet and of IFN-γ production, ILC1 is considered to be a close counterpart of Th1 cells. NK cells also express Tbet but can be distinguished from ILC1 cells, as the later do not express EOMES [111,112]. Besides NK cells, ILC1 is also reported as an important mediator of acute inflammatory responses in CHS. They produce Th1 dominant CHS responses parallel to $CD8^+$ T cells. The application of contact allergens like TNCB and oxazolone, induce type I contact hypersensitivity responses which are dominated by $CD8^+$ T, NK, and ILC1 cells [113,114]. Recently, Rafei-Shamsabadei *et al*. characterized the ear-infiltrating ILCs by studying CHS to TNCB in ILC reporter mice. Acute inflammatory responses appeared as early as 24 hours after allergen application and were characterized by elevated levels of NK and ILC1 cells [97]. ILC2 appeared in the later stage (48-72 h) with a characteristic type II cytokine production (IL-13 and IL-5). This indicated a function of ILC-2 in the resolution of the inflammatory response. The role of ILC2 was further investigated by using anti-CD90.2 mAb for depleting ILCs in $Rag1^{-/-}$ mice or by using $Ror\alpha^{sg/floxI}$ $l7r^{Cre/+}$ mice which lack ILC2 cells. Application of allergen in these mice showed significantly enhanced and prolonged inflammatory responses [97]. In conclusion, this data supports the effector function of ILC1 cells in type I CHS response, while ILC2 cells appear to exert regulatory functions to keep the immune response in a homeostatic balance.

ILC3 cells, on the other hand, share similarities with Th17 and Tc17 cells because of RORγt expression and production of type III cytokine such as IL-17 and IL-22 [115,116]. Such kind of IL-17 and IL-22 producing ILC3 cells were found to be involved in psoriasis [117,118]. During the developmental process, ILC3 bifurcates into two subtypes, namely $CCR6^+$ $ROR\gamma t^+$ cells and $CCR6^-$ $ROR\gamma t^+$ $Tbet^+$ cells. The $CCR6^+$ fraction of ILC3 cells comprise lymphoid tissue inducer (LTi) cells, which are important for the development of lymphoid organs at the embryonic stage [119-121]. In mice, the $CCR6^-$ fraction gradually loses RORγt expression and up regulates Tbet and converts into INFγ-producing cells resembling ILC1 cells [122,123]. Based on their production of type III cytokines and involvement in allergic skin diseases, the role of ILC3 cells in ACD needs to be investigated in more details.

CONCLUSION

Understanding the pathomechanism of ACD is

essential for the development of adequate therapies. Although T cells are major players in the clinical phase of the disease, their activation and maintenance of cytotoxic effects is dependent on innate immune cells. Identification of roles of NK cells and ILCs in the active phase of the disease may propose novel options for therapeutic interventions. Moreover, different cell types are involved in a context-dependent manner in ACD, which are believed to be linked with the type of allergen. It is established that the activity of Tregs can be manipulated for suppression of ACD, but identification of the homeostatic role of Tγδ17 cells and NK cells gave new insights into immunosuppressive functions in skin inflammation. Finally, it is obvious that ILCs are involved in ACD development, but there are many missing points to establish their networking with $CD4^+$ and $CD8^+$ T cells. Such gaps need to be filled to more precisely understand the interplay of the innate and adaptive immune system in ACD.

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