

Shifting Paradigms in Allergic Contact Dermatitis: The Role of Innate Immunity

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The role of the innate immune system in allergic contact dermatitis (ACD) has traditionally been confined to the initial antigen sensitization phase. However, more recent findings have shown the role of innate immunity in additional aspects of ACD, including the effector phase of the classic type IV hypersensitivity reaction. As a result, the precise immunologic mechanisms mediating ACD are more complex than previously believed. The aim of this review is to provide insight into recent advances in understanding the role of the innate immune system in the pathogenesis of ACD, including novel mechanistic roles for macrophages, innate lymphoid cells, natural killer cells, innate $\gamma\delta$ T cells, and other signaling molecules. These insights provide new opportunities for therapeutic intervention in ACD.

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INTRODUCTION

Allergic contact dermatitis (ACD) is the most common cause of occupationally related skin disease, affecting as many as 1 in 7 individuals annually (Kostner et al., 2017; Thyssen et al., 2009). Although the conceptual pathologic process in ACD is straightforward—an inappropriate or exaggerated immune response to skin contact with an otherwise innocuous substance—the precise immunologic mechanisms mediating this pathologic process are complex and incompletely understood. As a result, current therapies are limited to allergen avoidance, generalized suppression of the cutaneous immune response, and symptomatic relief (Nguyen et al., 2016). Here, we review recent findings in the realm of innate immunity that add to our understanding of the immunologic mechanisms of ACD and may allow for future therapeutic intervention.

DOGMA OF ACD

ACD is a classic cell-mediated hypersensitivity reaction in the skin, characterized by an initial sensitization phase and subsequent elicitation phase.

Phase I: sensitization

The sensitization or afferent phase is mediated by cells of the innate immune system. Sensitizers can include metal ions, such as nickel, gold, and cobalt, or low-molecular-weight chemicals, such as urushiol, found in poison ivy and mango skin (Davis et al., 2011). Sensitizing low-molecular-weight chemicals called *haptens* are nonimmunogenic but become recognizable by the immune system because of their ability to bind to proteins, a process called *haptization*. Dendritic cells (DCs) and Langerhans cells (LCs) have the intrinsic capacity to sense and recognize haptens and subsequently migrate from the skin to skin-draining lymph nodes. Antigenic encounter in the skin stimulates release of IL-1 β and tumor necrosis factor (TNF)- α by LCs and keratinocytes. These cytokines activate neutrophils and mast cells, resulting in the up-regulation of chemotactic factors, matrix metalloproteinases, and endothelial adhesion molecules, along with the down-regulation of epidermal adhesion factors (E-cadherin), leading to the migration of DCs and LCs to skin-draining lymph nodes (Enk et al., 1993; Enk and Katz, 1992).

Within the lymph node, antigen (Ag)-loaded major histocompatibility complexes are presented to naive CD4⁺ and CD8⁺ T cells, resulting in IFN- γ -secreting type 1 CD8⁺ cells and T helper (Th) type 1 cells, the classic effector cells of ACD (Dilulio et al., 1996; Gruschwitz and Hornstein, 1992; Kang et al., 1996; Luqman et al., 1992). The relative importance of each human skin-resident DC subset and LCs during the establishment of hapten-specific adaptive immune responses remains controversial. However, recent advances from murine and human ACD studies have shown distinct immune polarizations to potent Ag sensitizers, suggesting that distinct Ag-presenting cells may recognize specific Ag sensitizers and that these specific Ag-presenting cells may result in distinct immune responses (Dhingra et al., 2014; Igyarto et al., 2009; Kaplan et al., 2005; Mathers et al., 2009; Nakajima et al., 2012).

Phase II: elicitation

Phase II—the elicitation, effector, or efferent phase—represents the clinically relevant phase of ACD. In this phase, reexposure of sensitized individuals to the same antigen results in activation of innate cells such as keratinocytes, DCs, and LCs, including up-regulation of CXCL9, CXCL10, CCL17, CCL20, and CCL27, leading to the recruitment of previously formed Ag-specific (effector) memory T cells (Homey et al., 2000; Martin, 2012; Reiss et al., 2001). Although Ag-specific central memory T cells are recruited and participate in the delayed response, tissue-resident memory T cells are known to mediate rapid contact hypersensitivity (CHS) responses within 24 hours of elicitation (Gaide et al., 2015;

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Abbreviations: ACD, allergic contact dermatitis; Ag, antigen; Arg, arginase; CHS, contact hypersensitivity; DC, dendritic cell; ILC, innate lymphoid cell; iNOS, inducible nitric oxide synthase; LC, Langerhans cell; MMP, matrix metalloproteinase; MR, mannose receptor; NAAA, N-acyl ethanolamine acid amidase; NK, natural killer; TH, T helper; TNF, tumor necrosis factor

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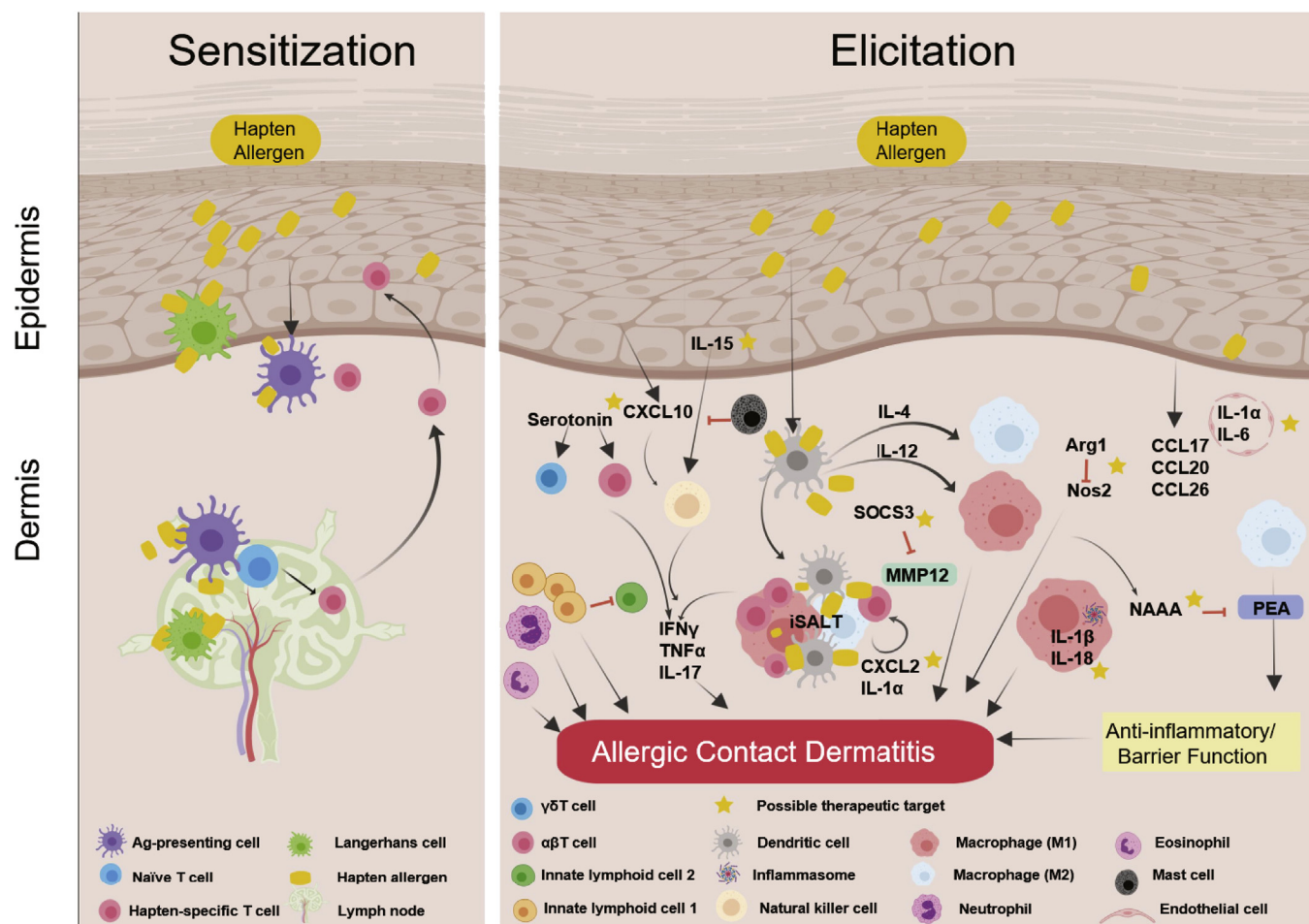


Figure 1. Integrated roles of innate immunity in the sensitization and elicitation phases of ACD. NK cells modulate sensitization and stimulate the CHS response with the formation of T-cell clusters. The inflammatory milieu of ACD ultimately results in the activation of both M1 and M2 macrophages, which via T-cell cluster formation, secretion of NAAA, and release of MMP-12 contribute to the CHS response. Stars denote specific therapeutic targets discussed in the text. ACD, allergic contact dermatitis; CHS, contact hypersensitivity; iSALT, inducible skin-associated lymphoid tissue; MMP, matrix metalloproteinase; NAAA, N-acylethanolamine acid amidase; NK, natural killer; PEA, palmitoylethanolamide; TNF, tumor necrosis factor.

Park and Kupper, 2015). T cells produce local IFN- γ , IL-17, IL-22, TNF- α , IL-4, and IL-13, further stimulating cytotoxic CD8⁺ effector T cells and innate immune cells, resulting in a type IV hypersensitivity reaction (Enk and Katz, 1992; Heufler et al., 1992; Kaplan et al., 2012; van Beelen et al., 2007).

Although the Ag-specific T cells in ACD are clearly pathogenic, it was previously believed that innate immune cells play a secondary, auxiliary role in mediating tissue damage in the elicitation phase of ACD. However, recent studies have shown that innate immune cells are in fact critical moderators of the efferent phase of ACD (Natsuaki et al., 2014; Suwanpradid et al., 2017b; Tuckermann et al., 2007). These novel mechanisms are illustrated in Figure 1.

INNATE IMMUNITY IN ACD

Macrophages

Macrophage subsets in ACD. Various cellular signals can cause bona fide macrophages and inflammatory Ly6c^{hi}CCR2⁺ monocytes to differentiate into classically activated (M1) or alternatively activated (M2) macrophages (Egawa et al., 2013; Jetten et al., 2014; Sica and Mantovani,

2012; Suwanpradid et al., 2017b; Tamoutounour et al., 2013).

M1 macrophages are stimulated by toll-like receptor ligands and IFN- γ , causing release of IL-6, IL-12, IL-23, IL-1 β , and TNF- α inflammatory cytokines (Colin et al., 2014; Sica and Mantovani, 2012). M1 macrophages play a proinflammatory role in direct damage to the affected epidermis and in the recruitment of other inflammatory cells and are found in large numbers in ACD skin lesions (Sica and Mantovani, 2012).

In contrast, alternatively activated M2 macrophages, induced via IL-4, IL-10, IL-13, glucocorticoid hormones, or vitamin D3, are typically involved in tissue remodeling, immunoregulatory functions, and wound healing through Th1 suppression (Akinrinmade et al., 2017; Colin et al., 2014; Jetten et al., 2014; Mantovani et al., 2002). However, under certain circumstances, proinflammatory cytokines such as TNF- α , IL-1, and IL-6 can all be produced by M2 macrophages, suggesting a potential role in inflammation (Arora et al., 2018; Kumamoto et al., 2016). The simultaneous, paradoxically pro- and anti-inflammatory, properties of M2 macrophages may be partially explained by the context of

Table 1. Potential therapeutic targets of innate immunity for the treatment of ACD

Potential Target	Mechanism	Inducer	Effect	Therapeutic Approach	Preclinical or Clinical Data
MMP-12	Extracellular matrix-degrading enzyme involved in tissue remodeling and wound repair	IL-4 and STAT6	CHS exacerbation measured in DNFB-induced murine model	Direct MMP-12 Inhibition	MMP408: Preclinical data in murine model (Li et al., 2009) FP-025: Phase 1 clinical trial (Foresee Pharmaceuticals, 2017)
SOCS3	Suppressor of cytokine signaling protein	IL-6, IL-10, IFN- γ	Diminishes MMP-12, decreasing CHS exacerbation	SOCS3 induction	INF- β induction of SOCS3 in multiple sclerosis patients: Phase I clinical trial (Ramgolan and Markovic-Plese, 2011)
Arg1	Enzyme that reduces <i>Nos2</i> -associated inflammation, (<i>Nos2</i> encodes iNOS)	Dexamethasone	Suppresses CHS, measured through DNFB hapten-induced mice	Arg1 induction	Pegylated recombinant human Arg1 in patients with hepatocellular carcinoma: Phase 1 clinical trial (Yau et al., 2015)
iSALT	Inducible skin-associated lymphoid tissue that stimulates chemokine signaling	TLR2, TLR4	Dendritic cells, keratinocytes, and mast cells release mediators (chemokines, IL-1 α , IL-1 β , IL-18) that stimulate cluster formation through CXCL2 release of M2 macrophages	CXCL2 inhibition	Preclinical murine studies only (Matsushita et al., 2014)
$\gamma\delta$ T cell	T-cell subtype that is able to produce cytokines regulating inflammation and tissue homeostasis	$\gamma\delta$ TCR	Mediates proinflammatory cytokines IFN- γ , TNF- α , and IL-12	$\gamma\delta$ T-cell inhibition	Preclinical trial of $\gamma\delta$ inhibitors in mice (Moore et al., 1996)
NAAA	Enzyme that catalyzes the degradation of PEA, an important regulator of innate immunity in humans	Present in macrophages and T lymphocytes	Decreased PEA stimulates DNFB-induced symptoms of pruritus, edema, and erythema	NAAA inhibition (ARN077)	ARN077: Preclinical development (Sasso et al., 2018)
NLRP3	Inflammasome in innate immune cells	NF- κ B, pro-IL-1 β , pro-IL-18	Activates caspase 1 and produces proinflammatory cytokines (IL-1 β) and IL-18	ASC, IL-18, IL-1 β inhibition	Anti-IL-1 β antibody (canakinumab) Anti-IL-18 antibody (GSK1070806) in Behçet disease: Phase 2 clinical trial (Smith, 2018)
NK cell population CD56 ^{high} CD16 [−] CD62L [−]	Innate immune lymphocytes	Stimulated when MHC class I or MHC class II molecules are not recognized	Increased expression of chemokines, CXCR3, CCR5, CCR6, IFN- γ release, and keratinocyte apoptosis, stimulating ACD	CD56 ^{high} CD16 [−] CD62L [−] NK cell inhibition via CXCL10	Anti-CXCL10 monoclonal antibody, MDX-1100 in patients with rheumatoid arthritis: Phase 2 clinical trial (Yellin et al., 2012)

Abbreviations: Arg, arginase; CHS, contact hypersensitivity; iNOS, inducible nitric oxide synthase; iSALT, inducible skin-associated lymphoid tissue; MHC, major histocompatibility complex; MMP, matrix metalloproteinase; NK, natural killer; PEA, palmitoylethanolamide; TCR, T-cell receptor; TLR, toll-like receptor.

their microenvironments and by further subdividing M2 macrophages into M2a, M2b, M2c, M2d, intermediate M1/M2, and tumor-resident macrophages, among others, each phenotypically different with varying, incompletely defined, roles in the innate immune response (Knudsen and Lee, 2016; Kumamoto et al., 2013; Nakagomi et al., 2015; Roszer, 2015; Tamoutounour et al., 2013). A murine model of DNFB-induced CHS showed the presence of a heterogeneous population of macrophages in lesional skin phenotypically consistent with M2a (arginase [Arg] 1⁺, mannose receptor [MR]⁺), M2c (receptor tyrosine kinase Mer⁺ [MerTK⁺]), tumor-resident macrophages (Arg1⁺, dectin-1⁺), and intermediate M1/M2 (CD301b⁺ and inducible nitric oxide synthase [iNOS⁺]Arg1⁺) macrophages (Kumamoto et al., 2013; Natsuaki et al., 2014; Suwanpradid et al., 2017b; Tamoutounour et al., 2013). Furthermore, intradermal

injection of bone marrow-derived macrophages into naive and CHS mice resulted in increased ear thickness, neutrophils, eosinophils, CD4⁺ T cells, and CD8⁺ T cells in lesional skin (Nakagomi et al., 2015). It remains unclear whether injection of such macrophages truly mimics a physiological response.

With regard to therapeutic targeting, MR⁺ (e.g., M2a) macrophages have been shown to favorably express matrix metalloproteinase (MMP) 12, resulting in enhanced production of CXCL1, CXCL2, and CCL2, often associated with an inflammatory response (Casella et al., 2016; Gong et al., 2017; Nakagomi et al., 2015). Indeed, genetic deletion or selective pharmacological inhibition of MMP-12 was found to suppress the inflammatory CHS response (Li et al., 2009; Nakagomi et al., 2015). Another MMP-12 inhibitor, FP-025, is currently in phase I clinical trials (Table 1) (Foresee Pharmaceuticals, 2017). Additionally, SOCS3 can be

induced by IL-6 and IFN- γ in MR⁺ macrophages and serves as a strong inhibitor of STAT6-mediated MMP-12 expression in macrophages and T helper cell differentiation (Christensen and Haase, 2012; Honda et al., 2013; Meguro et al., 2016; Nakagomi et al., 2015; Yoshimura et al., 2012). Thus, therapies inducing SOCS3 expression, favorably expressed in M2a macrophages, may provide benefit for patients with CHS via diminishing MMP-12 expression, thereby decreasing skin inflammation (Ekelund et al., 2006). Early data suggest that targeting SOCS3 has theoretical grounding in improving immune-driven cutaneous disease. In fact, a phase I clinical trial in multiple sclerosis has examined how IFN- β induces a tolerizing effect on DC–T-cell differentiation by inducing the expression of SOCS3 in DCs (Ramgolam and Markovic-Plese, 2011). These results could provide insight regarding the use of IFN- β or other pathway effectors as therapeutic targets in ACD.

Macrophage enzymes Arg1 and iNOS. In addition to the proinflammatory mechanisms involving MMP-12 and SOCS3 discussed, macrophage Arg1 and iNOS may play a pathogenic role in ACD, providing further insight into macrophage signaling and differentiation. Classically, iNOS (encoded by the *Nos2* gene) is known to be expressed in proinflammatory (e.g., M1) macrophages, whereas Arg1 is expressed in anti-inflammatory (e.g., M2a) macrophages, resulting in the production of nitric oxide and ornithine, respectively (Bruch-Gerharz et al., 2003). However, many Arg1-expressing macrophages often coexpress iNOS and Arg1. Furthermore, in addition to a reported reciprocal regulation of Arg1 and iNOS, these two effector molecules are also frequently induced subsequently and reactively to one another, suggesting an unclear hybrid and highly plastic phenotype with regard to traditional macrophage subclassifications.

Allergens were found to increase *Nos2* expression in macrophages (along with IL-6 and additional proinflammatory cytokines) while also increasing Arg1 (Honda et al., 2013; Kim et al., 2009; Suwanpradid et al., 2017b; Tamoutounour et al., 2013). Specific Arg1 deletion in lysosome M-expressing cells (including macrophages) aggravated CHS in an in vivo mouse model by increasing iNOS expression, a change that could be mitigated by pharmacologically inhibiting NOS. Additionally, *Nos2*^{−/−} mice showed significantly decreased CHS responses (Suwanpradid et al., 2017b). Together, excessive iNOS activity, derived from either M1, hybrid M1/M2 macrophages, or additional cells in CHS, leads to nitric oxide-induced proinflammatory cytokine production (Suwanpradid et al., 2017b). A phase I clinical trial of pegylated recombinant human Arg1 was studied in patients with advanced hepatocellular carcinoma and found it to be well tolerated with a favorable toxicity profile (Yau et al., 2015).

Macrophage lipid signaling. Macrophages and other skin defense cells generate biologically active lipids that modulate inflammation. Among these biologically active lipids is palmitoylethanolamide, a protective mediator of inflammation. Cysteine hydrolase N-acyl ethanolamine acid amidase (NAAA) catalyzes the degradation of palmitoylethanolamide, an agonist of peroxisome proliferator-activated receptor- α , an

important regulator of pain and innate immunity in humans (Gabrielsson et al., 2016). NAAA is 33%–35% identical to acid ceramidase, a cysteine amidase that hydrolyzes ceramides into fatty acid and sphingosine. Ceramides are key players in epidermal barrier function and were found to play a significant role in ACD (Jungersted and Agner, 2013; Zhu et al., 2011). The localization of NAAA in macrophages and T lymphocytes is suggestive of a role in regulating the immune system. Experimental animal and human models have proven that chronic inflammatory states (e.g., the effector phase of ACD) correlate with a decrease in palmitoylethanolamide levels because of impaired biosynthesis and increased NAAA (Ribeiro et al., 2015; Sasso et al., 2015; Zhu et al., 2011). Administration of the NAAA inhibitor ARN726 counteracts inflammation elicited by bacterial lipopolysaccharide, suggesting that the blockage of NAAA may be a therapeutic option for contact dermatitis (Ribeiro et al., 2015; Tsuboi et al., 2007). Furthermore, Sasso et al. (2018) studied the effects of the topical compound ARN077, a selective NAAA inhibitor, on DNFB-induced CHS responses. Results indicated that administration of ARN077 decreased DNFB-induced symptoms such as erythema, edema, and pruritus (Sasso et al., 2018). Additionally, mice lacking the NAAA enzyme also had a decreased DNFB response. With NAAA deletion, palmitoylethanolamide is not degraded, preventing a DNFB-induced dermatitis response. ARN077 was also found to normalize circulating Th2 cytokines, IL-4, IL-5, and IFN- γ levels (Sasso et al., 2018). These findings suggest that NAAA inhibitors such as ARN077 may also serve as potential therapeutic targets of innate immunity in ACD.

Inflammasome activation in CHS

Activation of the NLRP3 inflammasome in innate immune cells (e.g., macrophages) is a hallmark of toll-like receptor induction by many contact allergens such as nickel or monobenzene during the elicitation phase of ACD. The NLRP3 inflammasome consists of a multiprotein intracellular complex containing ASC and pro-caspase 1 that detects both pathogenic microorganisms and other stressors. NF- κ B is the upstream signaling pathway that promotes the transcription of NLRP3, as well as pro-IL-1 β and pro-IL-18, which are necessary for the inflammasome-mediated inflammatory response (Liu et al., 2017; Sutterwala et al., 2006; Watanabe et al., 2007; Weber et al., 2010). Ultimately, complex formation leads to caspase 1 activation and the processing and production of proinflammatory cytokines such as IL-1 β and IL-18, resulting in inflammation (Li and Zhong, 2014; Tschopp and Schroder, 2010; van den Boorn et al., 2016).

Given the involvement of the inflammasome in CHS, therapies targeting ASC, IL-18, and IL-1 β may serve as important therapeutic targets for severe ACD. Currently, an anti-IL-1 β antibody (canakinumab) is available for the treatment of autoinflammatory syndromes. Additionally, a phase II clinical trial of an anti-IL-18 antibody (GSK1070806) in Behçet disease is underway (Smith, 2018). Topical agents targeting inflammasome activation, such as NF- κ B decoys—found to be efficacious in a mouse model of atopic dermatitis—may represent an alternative approach with fewer systemic risks (Dajee et al., 2006).

Macrophages and inducible skin-associated lymphoid tissue

Inducible skin-associated lymphoid tissue consists of an aggregate of lymphoid cells that may also play a role in the elicitation phase of CHS (Ono and Kabashima, 2015). After hapten stimulation, dermal leukocytes form a cluster-like structure, predominantly around postcapillary venules (Natsuaki et al., 2014). Natsuaki et al. showed that DC–effector T-cell interactions are required for the induction of efficient Ag-specific immune responses in the skin (Honda and Kabashima, 2016; Natsuaki et al., 2014). Macrophages express IL-1 receptors and produce CXCL2 via IL-1 α stimulation (Natsuaki et al., 2014). Natsuaki et al. showed that the blockade of IL-1 α or CXCL2 reduces the formation of these clusters, T-cell activation, and subsequently CHS responses. These findings indicate that macrophages mediate cluster formation and that therapeutic targeting of CXCL2 may provide benefit in ACD, because decreased CXCL2 will decrease pathogenic DC–T-cell cluster formation (Honda et al., 2013; Honda and Kabashima, 2016). However, it remains unclear whether and how macrophages contribute to the long-term maintenance of such leukocyte clusters and to the propagation of pathogenic T cells in ACD patient skin. Future studies will be required to shed light on this important aspect of ACD.

Endothelial cells

Beyond cellular trafficking and provision of a clustering site for the formation of inducible skin-associated lymphoid tissue, endothelial cells likely play a contributing, if not key, role in the pathogenesis of ACD. With regard to the sensitization phase of ACD, endothelial cells have been shown to express toll-like receptors and major histocompatibility complexes I and II, suggesting a role as conditional antigen-presenting cells (Leeuwenberg et al., 1988; Opitz et al., 2009). Additionally, endothelial cells are known to produce proinflammatory molecules including IL-1 α , IL-6, and nitric oxide, among others. Corticosteroids are known to induce vasoconstriction and changes in endothelial protein expression, which may not only explain their efficacy but also highlight potential mechanisms of corticosteroid resistance in patients with ACD (Matsuda et al., 2008).

Innate lymphoid cells

Innate lymphoid cells (ILCs) show lymphoid morphology but lack Ag receptors and instead respond to various signals, such as cytokines, pathogen- or damage-associated molecular patterns, and other inflammatory signaling mediators. On the basis of cytokine production and transcription factor regulation, ILCs can be categorized into ILC1, ILC2, and ILC3 groupings, which parallel Th-cell subsets, with ILC2 the most prevalent in healthy skin (Spits et al., 2013). A recent study by Rafei-Shamsabadi et al. (2018) suggests a key role of ILCs in the elicitation phase of ACD. After allergen challenge in the murine CHS model, elevated numbers of ILC1 were detected in the skin, accompanied by increases in NK cells, IFN- γ , and TNF- α . Furthermore, depletion of ILC2 resulted in substantially increased ear-swelling responses (Rafei-Shamsabadi et al., 2018). ILC2 cells express high levels of Arg1 and increase after resolution of CHS (Bi et al., 2017; Monticelli et al., 2016; Rafei-Shamsabadi et al., 2018). We hope that future studies will shed light on the contribution of the ILC

Arg1/iNOS pathway to CHS responses. Taken together, these findings suggest that an imbalance favoring ILC1 subsets may partly explain the predisposition for ACD in select patients. Therapeutically, restoring the balance of ILCs may alleviate ACD. In a murine model, donor ILC2 infusions reduced the severity of acute graft versus host disease, also a Th1-driven disease (Bruce et al., 2017).

Natural killer cells

The inflammatory infiltrate in ACD, in addition to T lymphocytes, includes natural killer (NK) cells and NK-T lymphocytes. O'Leary et al. (2006) studied the direct role of NK cells in murine CHS by using Rag^{−/−} mice, which lack T cells but not NK cells. They identified an NK cell subpopulation, CD56^{high}CD16[−]CD62L[−] that is specifically recruited in inflamed skin through a CXCL10-dependent mechanism. Carbone et al. (2010) also identified this NK-cell subpopulation and found its involvement in ACD skin through the expression of CXCR3, CCR5, and CCR6 chemokine receptors. CD56^{high}CD16[−] cells exacerbate ACD reactions through the release of IFN- γ , TNF- α , and induction of keratinocyte apoptosis (Carbone et al., 2010). CD56^{high}CD16[−] NK cells also express secondary lymphoid organ receptors CCR7 and CD62L and are enriched in lymph nodes, where they modulate DC function and T-cell priming release (Campbell et al., 2001; Frey et al., 1998). These authors also showed that CHS to DNFB can be transferred via NK cells from DNFB-sensitized mice (O'Leary et al., 2006). DNFB elicited a strong CHS response in sensitized NK cells, whereas recipients of naive NK cells showed no CHS response. Thus, it was concluded that NK cells are necessary and sufficient for the transfer of hapten-specific memory from sensitized Rag2^{−/−} mice to naive recipients. The mechanism of hapten recognition by the NK cell subset, however, remains unclear. Although NK cells are a minority of the infiltrating lymphocytes (less than 10%), their contribution to the Th1-dominated microenvironment could be relevant, because NK cells release IFN- γ when exposed to T cell-derived cytokines (Carbone et al., 2010). Additionally, IL-15-deficient mice lacking NK cells show increased levels of ILC2 and ILC3 populations (Bi et al., 2017). Many of the cytokines mediating NK-cell activation may serve as future therapeutic targets in ACD.

$\gamma\delta$ T cells

$\gamma\delta$ T cells have innate-like features and are able to produce cytokines that regulate inflammation in response to tissue stress, including in murine models of ACD (Bonnevillie et al., 2010; Szczepanik et al., 1996). $\gamma\delta$ T-cell receptor–expressing cells have been shown to be involved in promoting CHS in mice, likely through the production of proinflammatory IFN- γ , IL-17A, TNF- α , and IL-12 and the auxiliary role of $\gamma\delta$ T cells in augmenting $\alpha\beta$ T-cell immunity (Nielsen et al., 2014; Ptak and Askenase, 1992; Shiohara et al., 1990; Strzepa et al., 2013; Welsh and Kripke, 1990). Drugs targeting $\gamma\delta$ T cells have been under investigation in sepsis immunosuppression, but none have been targeted for ACD (Yan, 2015). Skin-specific $\gamma\delta$ T cells constitute a far lower portion of the lymphocytes in human than in murine skin, yet whether the inflammatory infiltrate in human ACD

constitutes $\gamma\delta$ T cells as well remains unknown (Holderness et al., 2013; Suwanpradid et al., 2017a).

Mast cells, neutrophils, basophils, and eosinophils

Like other innate immune cells, mast cells are critical to the sensitization phase of ACD. Mast cells are observed in increased numbers in areas of chronic contact dermatitis, and recent evidence suggests that they may also be necessary during the elicitation phase (Dudeck et al., 2011; Honda et al., 2013). Specifically, mast cells may modulate chronic ACD via regulatory effects on CD8⁺ T-resident memory cells resulting from their ability to decrease IL-15 (Gimenez-Rivera et al., 2016).

Neutrophils, traditionally regarded as simple effector cells, are similarly emerging as players in both the sensitization and elicitation phases of ACD (Weber et al., 2015). Although depletion of neutrophils in mice results in decreased ear thickness in a model of ACD, the precise interactions occurring as a part of this regulation demand further study. Notably, neutrophils are thought to engage in cross-talk between both innate and adaptive immune cells, including macrophages, lymphocytes, and NK cells (Mantovani et al., 2011). It has been speculated that anti-CD90.2-mediated ILC depletion could be facilitated by the presence of neutrophils in the skin, reinforcing the complex role of both ILCs and neutrophils in ACD (Rafei-Shamsabadi et al., 2018).

Finally, basophils and eosinophils are known to play roles in nonclassical, Th2-mediated ACD (Lee et al., 2015; Mukai et al., 2009). Downstream results of eosinophil activation in this context have been linked with the neurosensory responses (e.g., pruritus) (Lee et al., 2015). Whether the roles of basophils and eosinophils extend to the elicitation phase of Th1 remains undetermined.

CONCLUSION

Traditionally, the role of innate immunity in ACD has been confined to the initial Ag-sensitization phase. However, more recent experimentation has clearly shown the integral role of innate immunity in numerous aspects of ACD, including the effector phase. Novel insights into the role and interactions among macrophages, T cells, NK cells, and other signaling molecules have not only clarified the mechanisms of pathogenesis (Figure 1) but have also outlined opportunities for future therapeutic approaches (Table 1). Ultimately, further work is needed to assess the feasibility of such therapies and determine the precise interplay among the various elements of both innate and adaptive immunity in ACD.

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CONFLICT OF INTEREST

ASM received funding for her laboratory from Silab Inc. in the past and is now consulting for this company. The content of this current work is unrelated to the consulting work. ARA received a Pfizer Independent Grant for Learning & Change, allowing salary support of a dermatitis fellow for 2 years. This grant does not provide any direct monetary value to ARA. All other authors state no conflict of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization: ASM, AKB; Project Administration: ASM; Funding Acquisition: ASM; Supervision: ASM; Visualization: JS, AKB, LRGH; Writing - Original Draft Preparation: AKB, LRGH, ASM; Writing - Review and Editing: AKB, LRGH, JS, ARA, ASM.

REFERENCES

- Akinrinmade OA, Chetty S, Daramola AK, Islam MU, Thepen T, Barth S. CD64: an attractive immunotherapeutic target for M1-type macrophage mediated chronic inflammatory diseases. *Biomedicine* 2017;5(3):56.
- Arora S, Dev K, Agarwal B, Das P, Syed MA. Macrophages: their role, activation and polarization in pulmonary diseases. *Immunobiology* 2018;223:383–96.
- Bi J, Cui L, Yu G, Yang X, Chen Y, Wan X. NK cells alleviate lung inflammation by negatively regulating group 2 innate lymphoid cells. *J Immunol* 2017;198:3336–44.
- Bonneville M, O'Brien RL, Born WK. $\gamma\delta$ T cell effector functions: a blend of innate programming and acquired plasticity. *Nat Rev Immunol* 2010;10:467–78.
- Bruce DW, Stefanski HE, Vincent BG, Dant TA, Reisdorf S, Bommasamy H, et al. Type 2 innate lymphoid cells treat and prevent acute gastrointestinal graft-versus-host disease. *J Clin Invest* 2017;127:1813–25.
- Bruch-Gerharz D, Schnorr O, Suschek C, Beck KF, Pfeilschifter J, Ruzicka T, et al. Arginase 1 overexpression in psoriasis: limitation of inducible nitric oxide synthase activity as a molecular mechanism for keratinocyte hyperproliferation. *Am J Pathol* 2003;162:203–11.
- Campbell JJ, Qin S, Unutmaz D, Soler D, Murphy KE, Hodge MR, et al. Unique subpopulations of CD56⁺ NK and NK-T peripheral blood lymphocytes identified by chemokine receptor expression repertoire. *J Immunol* 2001;166:6477–82.
- Carbone T, Nasorri F, Pennino D, Donnarumma M, Garcovich S, Eyerich K, et al. CD56 highCD16 - NK cell involvement in cutaneous lichen planus. *Eur J Dermatol* 2010;20:724–30.
- Casella G, Garzetti L, Gatta AT, Finardi A, Maiorino C, Ruffini F, et al. IL4 induces IL6-producing M2 macrophages associated to inhibition of neuroinflammation in vitro and in vivo. *J Neuroinflammation* 2016;13:139.
- Christensen AD, Haase C. Immunological mechanisms of contact hypersensitivity in mice. *APMIS* 2012;120:1–27.
- Colin S, Chinetti-Gbaguidi G, Staels B. Macrophage phenotypes in atherosclerosis. *Immunol Rev* 2014;262:153–66.
- Dajee M, Muchamuel T, Schryver B, Oo A, Alleman-Sposeto J, De Vry CG, et al. Blockade of experimental atopic dermatitis via topical NF- κ B decoy oligonucleotide. *J Invest Dermatol* 2006;126:1792–803.
- Davis MD, Wang MZ, Yiannias JA, Keeling JH, Connolly SM, Richardson DM, et al. Patch testing with a large series of metal allergens: findings from more than 1,000 patients in one decade at Mayo Clinic. *Dermatitis* 2011;22:256–71.
- Dhingra N, Shemer A, Correa da Rosa J, Rozenblit M, Fuentes-Duculan J, Gittler JK, et al. Molecular profiling of contact dermatitis skin identifies allergen-dependent differences in immune response. *J Allergy Clin Immunol* 2014;134:362–72.
- Dilulio NA, Xu H, Fairchild RL. Diversion of CD4⁺ T cell development from regulatory T helper to effector T helper cells alters the contact hypersensitivity response. *Eur J Immunol* 1996;26:2606–12.
- Dudeck A, Dudeck J, Scholten J, Petzold A, Surianarayanan S, Kohler A, et al. Mast cells are key promoters of contact allergy that mediate the adjuvant effects of haptens. *Immunity* 2011;34:973–84.
- Egawa M, Mukai K, Yoshikawa S, Iki M, Mukaida N, Kawano Y, et al. Inflammatory monocytes recruited to allergic skin acquire an anti-inflammatory M2 phenotype via basophil-derived interleukin-4. *Immunity* 2013;38:570–80.

- Ekelund E, Saaf A, Tengvall-Linder M, Melen E, Link J, Barker J, et al. Elevated expression and genetic association links the *SOCS3* gene to atopic dermatitis. *Am J Hum Genet* 2006;78:1060–5.
- Enk AH, Angeloni VL, Udey MC, Katz SI. An essential role for Langerhans cell-derived IL-1 beta in the initiation of primary immune responses in skin. *J Immunol* 1993;150:3698–704.
- Enk AH, Katz SI. Early molecular events in the induction phase of contact sensitivity. *Proc Natl Acad Sci USA* 1992;89:1398–402.
- Foresee Pharmaceuticals. A clinical study to evaluate the safety, tolerability, and pharmacokinetics of the MMP-12 inhibitor FP-025 after multiple oral ascending dose administration, and to evaluate the effect of food after a single oral dose administration in healthy subjects, <https://clinicaltrials.gov/ct2/show/NCT03304964>; 2017 (accessed 13 December 2018).
- Frey M, Packianathan NB, Fehniger TA, Ross ME, Wang WC, Stewart CC, et al. Differential expression and function of L-selectin on CD56^{bright} and CD56^{dim} natural killer cell subsets. *J Immunol* 1998;161:400–8.
- Gabrielsson L, Mattsson S, Fowler CJ. Palmitoylethanolamide for the treatment of pain: pharmacokinetics, safety and efficacy. *Br J Clin Pharmacol* 2016;82:932–42.
- Gaide O, Emerson RO, Jiang X, Gulati N, Nizza S, Desmarais C, et al. Common clonal origin of central and resident memory T cells following skin immunization. *Nat Med* 2015;21:647–53.
- Gimenez-Rivera VA, Siebenhaar F, Zimmermann C, Siiskonen H, Metz M, Maurer M. Mast cells limit the exacerbation of chronic allergic contact dermatitis in response to repeated allergen exposure. *J Immunol* 2016;197:4240–6.
- Gong M, Zhuo X, Ma A. STAT6 upregulation promotes M2 macrophage polarization to suppress atherosclerosis. *Med Sci Monit Basic Res* 2017;23:240–9.
- Gruschwitz MS, Hornstein OP. Expression of transforming growth factor type beta on human epidermal dendritic cells. *J Invest Dermatol* 1992;99:114–6.
- Heufler C, Topar G, Koch F, Trockenbacher B, Kampgen E, Romani N, et al. Cytokine gene expression in murine epidermal cell suspensions: interleukin 1 β and macrophage inflammatory protein 1 α are selectively expressed in Langerhans cells but are differentially regulated in culture. *J Exp Med* 1992;176:1221–6.
- Holderness J, Hedges JF, Ramstead A, Jutila MA. Comparative biology of $\gamma\delta$ T cell function in humans, mice, and domestic animals. *Annu Rev Anim Biosci* 2013;1:99–124.
- Homey B, Wang W, Soto H, Buchanan ME, Wiesenborn A, Catron D, et al. Cutting edge: the orphan chemokine receptor G protein-coupled receptor-2 (GPR-2, CCR10) binds the skin-associated chemokine CCL27 (CTACK/ALP/ILC). *J Immunol* 2000;164:3465–70.
- Honda T, Egawa G, Grabbe S, Kabashima K. Update of immune events in the murine contact hypersensitivity model: toward the understanding of allergic contact dermatitis. *J Invest Dermatol* 2013;133:303–15.
- Honda T, Kabashima K. Novel concept of iSALT (inducible skin-associated lymphoid tissue) in the elicitation of allergic contact dermatitis. *Proc Jpn Acad Ser B Phys Biol Sci* 2016;92:20–8.
- Igyarto BZ, Jenison MC, Dudda JC, Roers A, Muller W, Koni PA, et al. Langerhans cells suppress contact hypersensitivity responses via cognate CD4 interaction and langerhans cell-derived IL-10. *J Immunol* 2009;183:5085–93.
- Jetten N, Verbruggen S, Gijbels MJ, Post MJ, De Winther MP, Donners MM. Anti-inflammatory M2, but not pro-inflammatory M1 macrophages promote angiogenesis in vivo. *Angiogenesis* 2014;17:109–18.
- Jungstedt JM, Agner T. Eczema and ceramides: an update. *Contact Dermatitis* 2013;69:65–71.
- Kang K, Kubin M, Cooper KD, Lessin SR, Trinchieri G, Rook AH. IL-12 synthesis by human Langerhans cells. *J Immunol* 1996;156:1402–7.
- Kaplan DH, Igyarto BZ, Gaspari AA. Early immune events in the induction of allergic contact dermatitis. *Nat Rev Immunol* 2012;12:114–24.
- Kaplan DH, Jenison MC, Saeland S, Shlomchik WD, Shlomchik MJ. Epidermal Langerhans cell-deficient mice develop enhanced contact hypersensitivity. *Immunity* 2005;23:611–20.
- Kim D, Kim YJ, Seo JN, Kim J, Lee Y, Park CS, et al. 2,4-Dinitrofluorobenzene modifies cellular proteins and induces macrophage inflammatory protein-2 gene expression via reactive oxygen species production in RAW 264.7 cells. *Immunol Invest* 2009;38:132–52.
- Knudsen NH, Lee CH. Identity crisis: CD301b⁺ mononuclear phagocytes blur the M1-M2 macrophage line. *Immunity* 2016;45:461–3.
- Kostner L, Anzengruber F, Guilloid C, Recher M, Schmid-Grendelmeier P, Navarini AA. Allergic contact dermatitis. *Immunol Allergy Clin North Am* 2017;37:141–52.
- Kumamoto Y, Camporez JPG, Jurczak MJ, Shanabrough M, Horvath T, Shulman GI, et al. CD301b⁺ mononuclear phagocytes maintain positive energy balance through secretion of resistin-like molecule alpha. *Immunity* 2016;45:583–96.
- Kumamoto Y, Linehan M, Weinstein JS, Laidlaw BJ, Craft JE, Iwasaki A. CD301b⁺ dermal dendritic cells drive T helper 2 cell-mediated immunity. *Immunity* 2013;39:733–43.
- Lee JJ, Protheroe CA, Luo H, Ochkur SI, Scott GD, Zellner KR, et al. Eosinophil-dependent skin innervation and itching following contact toxicant exposure in mice. *J Allergy Clin Immunol* 2015;135:477–87.
- Leeuwenberg JF, Van Damme J, Meager T, Jeunhomme TM, Buurman WA. Effects of tumor necrosis factor on the interferon-gamma-induced major histocompatibility complex class II antigen expression by human endothelial cells. *Eur J Immunol* 1988;18:1469–72.
- Li W, Li J, Wu Y, Wu J, Hotchandani R, Cunningham K, et al. A selective matrix metalloproteinase 12 inhibitor for potential treatment of chronic obstructive pulmonary disease (COPD): discovery of (S)-2-(8-(methoxycarbonylamino)benzo[b,d]furan-3-sulfonamido)-3-methylbutanoic acid (MMP408). *J Med Chem* 2009;52:1799–802.
- Li X, Zhong F. Nickel induces interleukin-1 β secretion via the NLRP3–ASC–caspase-1 pathway. *Inflammation* 2014;37:457–66.
- Liu T, Zhang L, Joo D, Sun SC. NF- κ B signaling in inflammation. *Signal Transduct Target Ther* 2017;2:17023.
- Luqman M, Greenbaum L, Lu D, Bottomly K. Differential effect of interleukin 1 on naive and memory CD4⁺ T cells. *Eur J Immunol* 1992;22:95–100.
- Mantovani A, Cassatella MA, Costantini C, Jaillon S. Neutrophils in the activation and regulation of innate and adaptive immunity. *Nat Rev Immunol* 2011;11:519–31.
- Mantovani A, Sozzani S, Locati M, Allavena P, Sica A. Macrophage polarization: tumor-associated macrophages as a paradigm for polarized M2 mononuclear phagocytes. *Trends Immunol* 2002;23:549–55.
- Martin SF. Contact dermatitis: from pathomechanisms to immunotoxicology. *Exp Dermatol* 2012;21:382–9.
- Mathers AR, Janelins BM, Rubin JP, Tkacheva OA, Shufesky WJ, Watkins SC, et al. Differential capability of human cutaneous dendritic cell subsets to initiate Th17 responses. *J Immunol* 2009;182:921–33.
- Matsuda A, Orihara K, Fukuda S, Fujinaga H, Matsumoto K, Saito H. Corticosteroid enhances TNF- α -mediated leukocyte adhesion to pulmonary microvascular endothelial cells. *Allergy* 2008;63:1610–6.
- Matsushita H, Hijioka M, Ishibashi H, Anan J, Kurauchi Y, Hisatsune A, et al. Suppression of CXCL2 upregulation underlies the therapeutic effect of the retinoid Am80 on intracerebral hemorrhage in mice. *J Neurosci Res* 2014;92:1024–34.
- Meguro K, Nakagomi D, Suzuki K, Hosokawa J, Fukuta T, Yokota M, et al. SOCS3 expressed in M2 macrophages attenuates contact hypersensitivity by suppressing MMP-12 production. *J Invest Dermatol* 2016;136:649–57.
- Monticelli LA, Buck MD, Flamar A-L, Saenz SA, Tait Wojno ED, Yudanin NA, et al. Arginase 1 is an innate lymphoid-cell-intrinsic metabolic checkpoint controlling type 2 inflammation. *Nat Immunol* 2016;17:656–65.
- Moore TA, von Freeden-Jeffry U, Murray R, Zlotnik A. Inhibition of gamma delta T cell development and early thymocyte maturation in IL-7 $-/-$ mice. *J Immunol* 1996;157:2366–73.
- Mukai K, Obata K, Tsujimura Y, Karasuyama H. New insights into the roles for basophils in acute and chronic allergy. *Allergol Int* 2009;58:11–9.
- Nakagomi D, Suzuki K, Meguro K, Hosokawa J, Tamachi T, Takatori H, et al. Matrix metalloproteinase 12 is produced by M2 macrophages and plays important roles in the development of contact hypersensitivity. *J Allergy Clin Immunol* 2015;135:1397–400.
- Nakajima S, Igyarto BZ, Honda T, Egawa G, Otsuka A, Hara-Chikuma M, et al. Langerhans cells are critical in epicutaneous sensitization with protein antigen via thymic stromal lymphopoietin receptor signaling. *J Allergy Clin Immunol* 2012;129:1048–55.
- Natsuaki Y, Egawa G, Nakamizo S, Ono S, Hanakawa S, Okada T, et al. Perivascular leukocyte clusters are essential for efficient activation of effector T cells in the skin. *Nat Immunol* 2014;15:1064–9.

- Nguyen V, Simon L, Jaqua E. Allergic dermatoses. *Prim Care* 2016;43:433–49.
- Nielsen MM, Lovato P, MacLeod AS, Witherden DA, Skov L, Dyring-Andersen B, et al. IL-1 β -dependent activation of dendritic epidermal T cells in contact hypersensitivity. *J Immunol* 2014;192:2975–83.
- O'Leary JG, Goodarzi M, Drayton DL, von Andrian UH. T cell- and B cell-independent adaptive immunity mediated by natural killer cells. *Nat Immunol* 2006;7:507–16.
- Ono S, Kabashima K. Proposal of inducible skin-associated lymphoid tissue (ISALT). *Exp Dermatol* 2015;24:630–1.
- Opitz B, Eitel J, Meixenberger K, Suttrop N. Role of Toll-like receptors, NOD-like receptors and RIG-I-like receptors in endothelial cells and systemic infections. *Thromb Haemostasis* 2009;102:1103–9.
- Park CO, Kupper TS. The emerging role of resident memory T cells in protective immunity and inflammatory disease. *Nat Med* 2015;21:688–97.
- Ptak W, Askenase PW. Gamma delta T cells assist alpha beta T cells in adoptive transfer of contact sensitivity. *J Immunol* 1992;149:3503–8.
- Rafei-Shamsabadi DA, van de Poel S, Dorn B, Kunz S, Martin SF, Klose CSN, et al. Lack of type 2 innate lymphoid cells promotes a type I-driven enhanced immune response in contact hypersensitivity. *J Invest Dermatol* 2018;138:1962–72.
- Ramgolam VS, Markovic-Plese S. Regulation of suppressors of cytokine signaling as a therapeutic approach in autoimmune diseases, with an emphasis on multiple sclerosis. *J Signal Transduct* 2011;2011:635721.
- Reiss Y, Proudfoot AE, Power CA, Campbell JJ, Butcher EC. CC chemokine receptor (CCR)4 and the CCR10 ligand cutaneous T cell-attracting chemokine (CTACK) in lymphocyte trafficking to inflamed skin. *J Exp Med* 2001;194:1541–7.
- Ribeiro A, Pontis S, Mengatto L, Armirotti A, Chiurchiu V, Capurro V, et al. A potent systemically active *N*-acylethanolamine acid amidase inhibitor that suppresses inflammation and human macrophage activation. *ACS Chem Biol* 2015;10:1838–46.
- Roszer T. Understanding the mysterious M2 macrophage through activation markers and effector mechanisms. *Mediators Inflamm* 2015;2015:816460.
- Sasso O, Migliore M, Habrant D, Armirotti A, Albani C, Summa M, et al. Multitarget fatty acid amide hydrolase/cyclooxygenase blockade suppresses intestinal inflammation and protects against nonsteroidal anti-inflammatory drug-dependent gastrointestinal damage. *FASEB J* 2015;29:2616–27.
- Sasso O, Summa M, Armirotti A, Pontis S, De Mei C, Piomelli D. The *N*-acylethanolamine acid amidase inhibitor ARN077 suppresses inflammation and pruritus in a mouse model of allergic dermatitis. *J Invest Dermatol* 2018;138:562–9.
- Shiohara T, Moriya N, Gotoh C, Hayakawa J, Nagashima M, Saizawa K, et al. Loss of epidermal integrity by T cell-mediated attack induces long-term local resistance to subsequent attack. I. Induction of resistance correlates with increases in Thy-1+ epidermal cell numbers. *J Exp Med* 1990;171:1027–41.
- Sica A, Mantovani A. Macrophage plasticity and polarization: in vivo veritas. *J Clin Invest* 2012;122:787–95.
- Smith R. An experimental medicine study to characterise the importance of IL-18 production and to evaluate the therapeutic potential of IL-18 blockade with GSK1070806 in subjects with Behcet's disease, <https://clinicaltrials.gov/ct2/show/NCT03522662>; 2018 (accessed 12 April 2019).
- Spits H, Artis D, Colonna M, Dieffenbach A, Di Santo JP, Eberl G, et al. Innate lymphoid cells—a proposal for uniform nomenclature. *Nat Rev Immunol* 2013;13:145–9.
- Strzepa A, Majewska-Szczepanik M, Szczepanik M. $\gamma\delta$ T cells positively regulate contact sensitivity (CS) reaction via modulation of INF- γ , IL-12 and TNF- α production. *Folia Biol* 2013;61:205–10.
- Sutterwala FS, Ogura Y, Szczepanik M, Lara-Tejero M, Lichtenberger GS, Grant EP, et al. Critical role for NALP3/CIAS1/cryopyrin in innate and adaptive immunity through its regulation of caspase-1. *Immunity* 2006;24:317–27.
- Suwanpradit J, Holcomb ZE, MacLeod AS. Emerging skin T-cell functions in response to environmental insults. *J Invest Dermatol* 2017a;137:288–94.
- Suwanpradit J, Shih M, Pontius L, Yang B, Birukova A, Guttman-Yassky E, et al. Arginase1 deficiency in monocytes/macrophages upregulates inducible nitric oxide synthase to promote cutaneous contact hypersensitivity. *J Immunol* 2017b;199:1827–34.
- Szczepanik M, Anderson LR, Ushio H, Ptak W, Owen MJ, Hayday AC, et al. Gamma delta T cells from tolerized alpha beta T cell receptor (TCR)-deficient mice inhibit contact sensitivity-effector T cells in vivo, and their interferon-gamma production in vitro. *J Exp Med* 1996;184:2129–39.
- Tamoutounour S, Guillemins M, Montanana Sanchis F, Liu H, Terhorst D, Malosse C, et al. Origins and functional specialization of macrophages and of conventional and monocyte-derived dendritic cells in mouse skin. *Immunity* 2013;39:925–38.
- Thyssen JP, Linneberg A, Menne T, Nielsen NH, Johansen JD. Contact allergy to allergens of the TRUE-test (panels 1 and 2) has decreased modestly in the general population. *Br J Dermatol* 2009;161:1124–9.
- Tschopp J, Schroder K. NLRP3 inflammasome activation: the convergence of multiple signalling pathways on ROS production? *Nat Rev Immunol* 2010;10:210–5.
- Tsuboi K, Takezaki N, Ueda N. The *N*-acylethanolamine-hydrolyzing acid amidase (NAAA). *Chem Biodivers* 2007;4:1914–25.
- Tuckermann JP, Kleiman A, Moriggl R, Spanbroek R, Neumann A, Illing A, et al. Macrophages and neutrophils are the targets for immune suppression by glucocorticoids in contact allergy. *J Clin Invest* 2007;117:1381–90.
- van Beelen AJ, Teunissen MB, Kapsenberg ML, de Jong EC. Interleukin-17 in inflammatory skin disorders. *Curr Opin Allergy Clin Immunol* 2007;7:374–81.
- van den Boorn JG, Jakobs C, Hagen C, Renn M, Luiten RM, Melief CJ, et al. Inflammasome-dependent induction of adaptive NK cell memory. *Immunity* 2016;44:1406–21.
- Watanabe H, Gaide O, Petrilli V, Martinon F, Contassot E, Roques S, et al. Activation of the IL-1 β -processing inflammasome is involved in contact hypersensitivity. *J Invest Dermatol* 2007;127:1956–63.
- Weber FC, Esser PR, Muller T, Ganesan J, Pellegatti P, Simon MM, et al. Lack of the purinergic receptor P2X $_7$ results in resistance to contact hypersensitivity. *J Exp Med* 2010;207:2609–19.
- Weber FC, Nemeth T, Csepregi JZ, Dudeck A, Roers A, Ozsvari B, et al. Neutrophils are required for both the sensitization and elicitation phase of contact hypersensitivity. *J Exp Med* 2015;212:15–22.
- Welsh EA, Kripke ML. Murine Thy-1+ dendritic epidermal cells induce immunologic tolerance in vivo. *J Immunol* 1990;144:883–91.
- Yan K. Role of gamma delta T cells in sepsis immunosuppression and its molecular mechanism, NCT02361970, <https://clinicaltrials.gov/ct2/show/NCT02361970>; 2015 (accessed 12 December 2018).
- Yau T, Cheng PN, Chan P, Chen L, Yuen J, Pang R, et al. Preliminary efficacy, safety, pharmacokinetics, pharmacodynamics and quality of life study of pegylated recombinant human arginase 1 in patients with advanced hepatocellular carcinoma. *Invest New Drugs* 2015;33:496–504.
- Yellin M, Paliienko I, Balanescu A, Ter-Vartanian S, Tseluyko V, Xu LA, et al. A phase II, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of MDX-1100, a fully human anti-CXCL10 monoclonal antibody, in combination with methotrexate in patients with rheumatoid arthritis. *Arthritis Rheum* 2012;64:1730–9.
- Yoshimura A, Suzuki M, Sakaguchi R, Hanada T, Yasukawa H. SOCS, inflammation, and autoimmunity. *Front Immunol* 2012;3:20.
- Zhu C, Solorzano C, Sahar S, Realini N, Fung E, Sassone-Corsi P, et al. Proinflammatory stimuli control *N*-acylphosphatidylethanolamine-specific phospholipase D expression in macrophages. *Mol Pharmacol* 2011;79:786–92.