

Review Article

Cytokines and Chemokines in Irritant Contact Dermatitis

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Irritant contact dermatitis is a result of activated innate immune response to various external stimuli and consists of complex interplay which involves skin barrier disruption, cellular changes, and release of proinflammatory mediators. In this review, we will focus on key cytokines and chemokines involved in the pathogenesis of irritant contact dermatitis and also contrast the differences between allergic contact dermatitis and irritant contact dermatitis.

1. Introduction

Irritant contact dermatitis (ICD) is an inflammatory response of the skin to various external stimuli. It arises as a result of activated innate immunity to direct injury of the skin without prior sensitization [1–3]. ICD is a complex reaction modulated by both intrinsic and extrinsic factors [2–4]. Intrinsic factors which influence the susceptibility to ICD include genetic predisposition, for example, atopic diathesis, age, sex, and body region. Extrinsic factors include the inherent nature of the irritants, exposure volume, concentration, duration, repetition, and the presence of further environmental and mechanical factors.

ICD has a spectrum of clinical features which can be divided into several different categories depending on the irritant and its exposure pattern. Ten clinical subtypes have been proposed [2]. The influence of irritants on various cytokines/chemokines has not been well delineated so far, although it is plausible that different environmental insults and the subsequent variation in cytokines/chemokines expression could result in distinct clinical phenotypes.

In this review, we discuss the pathophysiological mechanisms involved in ICD with a focus on key cytokines and chemokines as well as their cellular source in the skin. Furthermore, we highlight the key differences between ICD and allergic contact dermatitis (ACD).

2. Pathophysiology of Irritant Contact Dermatitis

Previously thought of as an immunologic inert process, at present there is increasing evidence showing that ICD is a complex, interlinked process involving perturbations in the skin barrier integrity, cellular changes, and release of various proinflammatory mediators [5, 6].

2.1. Irritants and Skin Barrier Integrity. Integrity of the epidermal barrier function plays an important role in the interaction and the response of the human skin to irritants [7]. Patients with atopic dermatitis are known to have an epidermal barrier dysfunction and have an augmented response to various exogenous irritants [8]. In particular, atopic dermatitis and filaggrin null alleles are associated with an increased susceptibility and severity to ICD [9, 10]. Recently, it has been shown that filaggrin loss-of-function mutation is associated with an enhanced expression of IL-1, which plays a central role in the initiation of ICD [11].

The mechanisms leading to damage of the skin barrier are also dependent on the intrinsic nature of the irritant. Organic solvents such as acetone can extract lipids from the stratum corneum, thereby leading to disruption of the epidermal barrier [12]. Anionic surfactants like sodium lauryl

sulphate (SLS) can damage protein structures such as keratin, involucrin, profilaggrin, and loricrin, exposing new water binding sites and causing hyperhydration of the stratum corneum and disorganization of the lipid bilayers [13–16]. The end result of this damage to the skin barrier is the activation of the innate immunity with its cellular changes and production of proinflammatory cytokines, such as IL-1 α . Simultaneously, barrier disruption also induces reparative processes to restore homeostasis [17].

2.2. Key Cellular Components and Mediators in ICD

2.2.1. Keratinocytes. Keratinocytes play a major role in the production of immune mediators in ICD. The disruption of the skin barrier leads to release of preformed IL-1 α [18], which represents an initial step in the inflammatory cascade of ICD. Numerous *in vitro* studies have also shown that various irritants induce IL-1 α expression in keratinocytes [5, 6, 19–22]. Activation of IL-1 α is subsequently thought to stimulate further production of proinflammatory cytokines and chemokines such as IL-1 β , TNF- α , IL-6, and CXCL8 (IL-8) by surrounding epidermal and dermal cells [23, 24].

Unlike IL-1 α , which is constitutively produced, IL-1 β is secreted as a biologically inactive precursor that is cleaved into an active 17.5 kDa molecule by a protease not normally present in resting keratinocytes [25]. IL-1 β -converting enzyme (ICE) is a unique processing enzyme involved in the production of active IL-1 β . In activated keratinocytes, ICE has been readily detected following incubation with irritants such as phorbol myristate acetate (PMA) or SLS [26], indicating that activation of ICE may represent a key pathogenic step in ICD elicited through certain irritants.

Together with IL-1 α , the subsequent actions of IL-1 β are pleiotropic and involve activation of dendritic cells and T cells, further cytokine and chemokine production, and upregulation of adhesion molecules such as ICAM-1 on endothelial cells and fibroblasts [5, 6, 24], which can all lead to perpetuation of cutaneous inflammation.

Another key cytokine in ICD is TNF- α . Upregulation of TNF- α in the skin has been reported following application of irritants such as dimethyl sulfoxide, PMA, formaldehyde, tributyltin, and SLS [20, 27–29]. Moreover, the importance of TNF- α in ICD has previously been demonstrated in irritant reactions which were inhibited *in vivo* by administration of antibodies to TNF [30]. The effects of TNF- α are also pleiotropic, leading to increased expression of major histocompatibility complex class II molecules, upregulation of cell adhesion molecules such as ICAM-1 on keratinocyte and endothelial cells [31, 32], and further induction of inflammatory mediators such as IL-1, IL-6, GM-CSF, IFN- γ , and CXCL8 [23, 33]. In addition, TNF- α in concert with IL-1 α particularly acts as primary alarm signals, which triggers the release of secondary CCL20 (Macrophage Inflammatory Protein-3) and CXCL8 chemokine signals [34, 35]. These increased levels of CCL20 and CXCL8 have the potential to initiate infiltration of immune cells such as CCR6+ T cells and immature dendritic cells into an area of the skin that is exposed to the irritant [36].

Further support for a central role of IL-1 α and TNF- α in the pathogenesis of ICD include recent studies which have shown that certain genetic polymorphisms are associated with increased or decreased risk of developing ICD. Individuals with TNFA-238 polymorphisms have a reduced risk of developing ICD whereas individuals with TNFA-308 alleles have an increased risk of ICD [37]. Similarly, individuals with IL1A-889 C/T polymorphisms are associated with a protective effect to the development of ICD [38].

Other cytokines and factors that have been implicated in the pathogenesis of ICD and which are also produced by keratinocytes include vascular endothelial growth factor (VEGF) [21, 39, 40] and IL-6 [19, 27, 39]. VEGF which is mainly secreted by keratinocytes is a potent mediator of angiogenesis that stimulates the migration and proliferation of endothelial cells, facilitates vascular permeability, and induces the expression of adhesion molecules ICAM-1 and VCAM-1 on endothelial cells [39]. IL-6, which is upregulated by various irritants, induces infiltration of mononuclear cell and is believed to play an important role in perpetuating skin inflammation. However, a recent study has shown that IL-6 may also exert some anti-inflammatory effects in ICD and that these effects may be dependent on the chemical nature of the irritant [41]. Furthermore, counterregulatory cytokines such as IL-10 [27, 42] and IL-1 receptor antagonists [21] especially in repeated irritant application are also produced to limit inflammation.

2.2.2. Fibroblasts. Dermal involvement is common in ICD due to either penetration of the irritant chemical to the dermis or indirectly through mediators derived from keratinocytes. Fibroblasts have been associated with maintaining homeostasis of the skin immune system by their interactions with the keratinocytes. The release of keratinocytes derived IL-1 α activates fibroblasts to release other active mediators such as CXCL8, CXCL1 (GRO- α), and CCL2 (monocyte chemotactic protein-1/MCP-1) [43]. In addition, TNF- α dependent secretion of CCL2 and CCL5 (RANTES) plays a role in initiating migration of irritant-exposed human Langerhans cells (LCs) out of the epidermis [44–46].

2.2.3. Endothelial Cells. Following exposures to irritants, there is an upregulation of adhesion molecules and chemokines on endothelial cells which can facilitate the migration of further immune cells like dendritic cells, macrophages, and T cells into the skin. Interestingly, CCL21 has been reported to be upregulated on dermal lymphatic endothelial cells in ICD [47]. This is thought to facilitate the emigration of CCR7+ dendritic cells (DCs) from the skin.

2.2.4. Dendritic Cells. The role of DCs and their cytokines in ICD is not well characterized. Epidermal LCs have been shown to migrate into the dermis after topical exposure of irritants to the skin, despite the supposed independence of ICD from adaptive immunity [44, 48]. This migration is likely to occur due to the upregulation of IL-1 and TNF- α by irritants. Furthermore, migration to the dermis occurs under the influence of CCL2 (MCP-1) and CCL5 (RANTES),

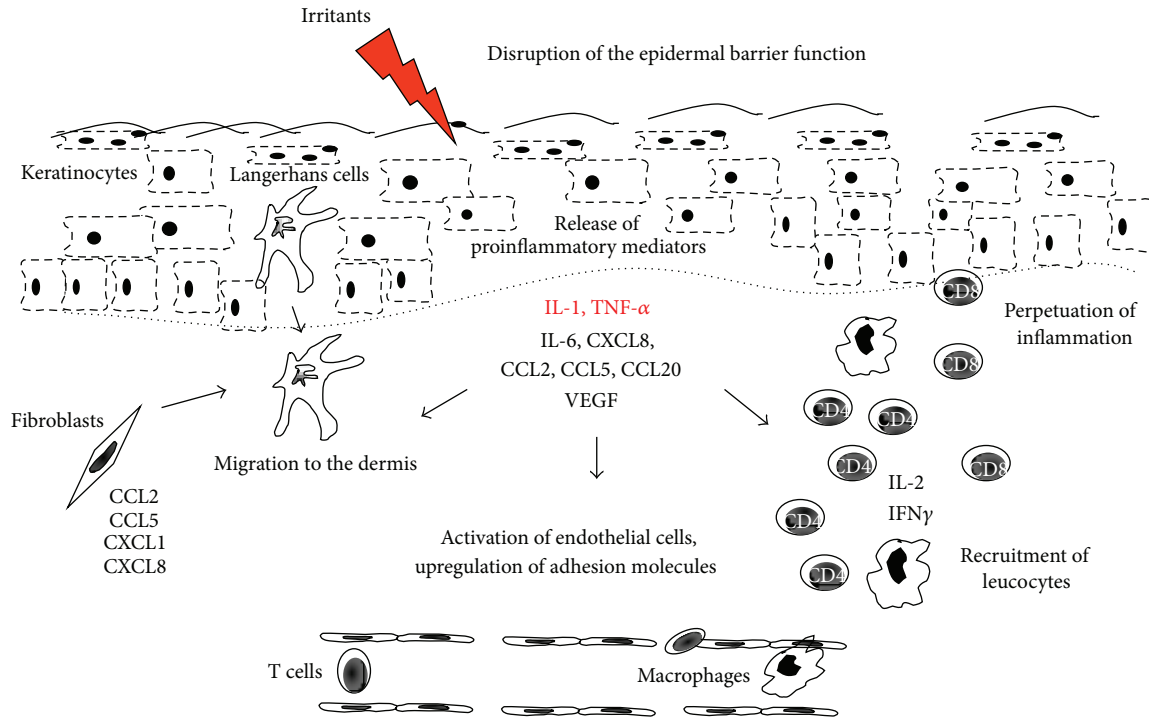


FIGURE 1: Immunological mechanisms in irritant contact dermatitis. Following irritant insult, there is disruption of the epidermal barrier with release of proinflammatory mediators, that is, IL-1 and TNF- α . This results in stimulation of further cytokine and chemokines production, for example, by keratinocytes, fibroblasts, and endothelial cells, upregulation of adhesion molecules on endothelial cells, and the subsequent recruitment of leucocytes thereby perpetuating ongoing inflammation.

which are secreted by fibroblasts [44]. In addition, it has been shown that there is an IL-10 dependent postmigration phenotypic switch from CD1a⁺ LCs into CD14⁺CD68⁺ macrophage-like cells in ICD [46]. The significance of this migration and phenotypic switch is unclear although it is postulated that this is an important escape mechanism to protect LCs from cell death by harmful toxic agents. These transformed CD14⁺CD68⁺ macrophages may also have a role in rapidly removing damaged tissue as a result of skin barrier disruption, and lastly this phenotypic switch may also serve to maintain immunological ignorance, thereby avoiding the generation of collateral autoimmunity [46].

2.2.5. Lymphocytes. The role of skin infiltrating T lymphocytes in ICD is also not well defined. In acute reactions of ICD, cellular infiltrates consisting of mainly CD4⁺ lymphocytes are seen with an increased level of IL-2 and IFN- γ (Th1-associated cytokines) as well as CD8⁺ cytotoxic T cells [20, 49]. However, it has been shown that Th1 associated CXCR3 ligands such as CXCL9, 10, and 11 are among the most differentially expressed chemokines discriminating between ICD and ACD [50]. These chemokines were expressed at significantly lower levels in ICD compared to ACD. Further studies would be needed to clarify the role and subsets of T lymphocytes involved. Recently, Th17 cells which are novel subset of CD4⁺ T cells have been shown to be implicated in the pathogenesis of ACD. These T-cell subsets induce chemokine and cytokine release from keratinocytes and

intensify the ICAM-1 dependent keratinocytes T-cell interaction thus promoting nonspecific T-cell-induced apoptosis. At present, it remains unclear if a similar mechanism exists for ICD [51–53].

2.3. Summary of Cytokines/Chemokines Activation Cascade in ICD. Although the precise cytokines/chemokines activation cascade in ICD is still unclear, it is likely that the primary cytokines involved following irritant exposure are IL-1 and TNF- α . The synergistic effects of these two cytokines result in the further activation and release of secondary cytokines/chemokines such as IL-2, IL-6, GM-CSF, IFN- γ , VEGF, CXCL8, CCL2, CCL5, and CCL20 and expression of cell adhesion molecules [4, 5, 23, 30, 31]. A postulated model is shown in Figure 1. The various cytokines/chemokines and mediators involved in ICD are also summarized in Table 1. The myriad of cytokines and cell types involved in ICD demonstrates that the complexity of the skin response to irritants and interindividual variations in the level of cytokines present or produced in the skin is likely responsible for the nature of irritants and intensity of the irritation reaction.

3. Comparison between ACD and ICD

Despite some distinct pathological differences, many common features such as certain histopathological (e.g., cellular infiltrate, vasodilatation) and molecular (e.g., cytokines/chemokines production, upregulation of endothelial adhesion

TABLE 1: Key cytokines and chemokines involved in ICD.

Cytokine	Source	Function
Interleukin-1	Keratinocytes Langerhans cells/dendritic cells Monocytes/macrophages T cells Endothelial cells	Proinflammatory Chemoattractant for T and B cells Upregulates adhesion molecule Induces IL-1, IL-2, IL-4, IL-6, IFN- γ , CXCL8, and CCL20 Aids Langerhans cell migration
Interleukin-6	Keratinocytes Langerhans cells/dendritic cells Monocytes/macrophages Fibroblasts Endothelial cells	Proinflammatory Chemotactic for neutrophils and T cells Keratinocyte proliferation
Interleukin-8 (CXCL8)	Keratinocytes Monocytes/macrophages Fibroblasts Neutrophils T cells Endothelial cells Lymphocytes	Proinflammatory Chemotaxis Activation of neutrophils Basophil release of histamine
Interleukin-10	Keratinocytes T cells	Anti-inflammatory Inhibits production of IL-1 α , IL-1 β , IL-2, IL-3, IL-6, IL-8, TNF- α , MIP-1 α , IFN- γ , M-CSF, and GM-CSF Downregulates MHC class II Downregulates adhesion molecules
GM-CSF	Keratinocytes Melanocytes T cells Endothelial cells Mast cells	Proinflammatory Enhances effector function of monocytes and neutrophils
IFN- γ	Lymphocytes Keratinocytes	Proinflammatory Induces/enhances MHC class II Upregulates cellular adhesion molecules
TNF- α	Keratinocytes Dendritic cells Monocytes/macrophages Mast cells Fibroblasts Lymphocytes	Proinflammatory Activates T cells, macrophages, and granulocytes Upregulates MHC classes I and II Induces IL-1, IL-6, IL-8, TNF, GM-CSF, M-CSF, G-CSF, PDGF, and VEGF Cellular adhesion molecule expression
VEGF	Keratinocytes	Proinflammatory Induces endothelial cell permeability Promotes angiogenesis Increases expression of adhesion molecules Promotes monocyte migration
CCL2 (MCP-1)	Monocytes/macrophages Dendritic cells Fibroblasts	Chemotactic for monocytes, T cells, and dendritic cells
CCL5 (RANTES)	Keratinocytes Dendritic cells Fibroblasts Mast cells	Chemotactic for T cells, eosinophils, and basophils
CCL20 (MIP-3)	Keratinocytes Lymphocytes Fibroblasts Monocytes	Chemotactic for dendritic cells, lymphocytes, and neutrophils

Adapted and modified from Smith et al. [5].

molecules) alterations exist between ICD and ACD [54, 55]. Such similarities have also been attributed to the irritant potential of allergens which strongly contributes to their allergenicity [56]. In the early phases, it is likely that IL-1 and TNF- α driven innate immune responses are involved in both ICD and ACD. In later phases of ICD, skin inflammation is still critically dependent on innate responses. However, in ACD adaptive immune responses involving antigen-specific T cells take over to amplify skin inflammation [50]. In recent years, some molecular differences between ICD and ACD have been identified. In particular, CXCR4 and CCR7 expressions on LCs have been shown to be upregulated after allergen but not by irritant exposure [46]. CXCR4 and CCR7 are important chemokine receptors which facilitate allergen-induced LC migration toward the lymph vessels via a two-step CXCR4-CXCL12 and CCR7-CCL19/CCL21 interaction [57]. Moreover, the expression of CXCL9, CXCL10, and CXCL11 has been shown to be specifically upregulated in ACD [50]. In addition, *in vitro* studies using monocyte-derived DCs have shown that certain phenotypic alterations of immature DCs such as upregulation of surface expression markers (CD54, CD86, and HLA-DR) as well as production of IL-1 β [58] and CXCL8 [59] are increased in ACD compared to ICD. Previous studies involving gene expression analysis have also demonstrated that allergens but not irritants may lead to upregulation of certain genes such as CCL23, CCL4, CYP27A1, HML2, NOTCH3, SI00A4, and SLAM in DCs, thus providing the basis for approaches to identify skin-sensitizing chemicals [60].

4. Conclusion

Although the precise pathomechanisms of ICD still remain to be elucidated, there is increasing evidence that a myriad of cytokines and chemokines as well as immune cells are actively involved in ICD. Greater understanding of these mechanisms and differences between ACD and ICD will aid in the evaluation of irritants and assessment of skin damage as well as therapeutics.

Conflict of Interests

The authors declare that they have no conflict of interests.

References

- [1] S. Gibbs, "In vitro irritation models and immune reactions," *Skin Pharmacology and Physiology*, vol. 22, no. 2, pp. 103–113, 2009.
- [2] A. Chew and H. I. Maibach, "Occupational issues of irritant contact dermatitis," *International Archives of Occupational and Environmental Health*, vol. 76, no. 5, pp. 339–346, 2003.
- [3] A. L. Chew and H. I. Maibach, "Ten genotypes of irritant contact dermatitis," in *Contact Dermatitis*, A. L. Chew and H. I. Maibach, Eds., pp. 5–9, Springer, Berlin, Germany, 2006.
- [4] D. Slodownik, A. Lee, and R. Nixon, "Irritant contact dermatitis: a review," *Australasian Journal of Dermatology*, vol. 49, no. 1, pp. 1–11, 2008.
- [5] H. R. Smith, D. A. Basketter, and J. P. McFadden, "Irritant dermatitis, irritancy and its role in allergic contact dermatitis," *Clinical and Experimental Dermatology*, vol. 27, no. 2, pp. 138–146, 2002.
- [6] S. Lisby and O. Baadsgaard, "Mechanisms of irritant contact dermatitis," in *Contact Dermatitis*, P. J. Frosch, T. Menné, and J. P. Lepoittevin, Eds., pp. 69–82, Springer, Berlin, Germany, 2006.
- [7] J. W. Fluhr, R. Darlenski, I. Angelova-Fischer, N. Tsankov, and D. Basketter, "Skin irritation and sensitization: mechanisms and new approaches for risk assessment. 1. Skin irritation," *Skin Pharmacology and Physiology*, vol. 21, no. 3, pp. 124–135, 2008.
- [8] M. J. Cork, D. A. Robinson, Y. Vasilopoulos et al., "New perspectives on epidermal barrier dysfunction in atopic dermatitis: gene-environment interactions," *Journal of Allergy and Clinical Immunology*, vol. 118, no. 1, pp. 3–21, 2006.
- [9] M. J. Visser, L. Landeck, L. E. Campbell et al., "Impact of atopic dermatitis and loss-of-function mutations in the filaggrin gene on the development of occupational irritant contact dermatitis," *The British Journal of Dermatology*, vol. 168, no. 2, pp. 326–332, 2013.
- [10] J. A. Davis, M. O. Visscher, R. R. Wickett, and S. B. Hoath, "Influence of tumour necrosis factor- α polymorphism-308 and atopy on irritant contact dermatitis in healthcare workers," *Contact Dermatitis*, vol. 63, no. 6, pp. 320–332, 2010.
- [11] S. Kezic, G. M. O'Regan, R. Lutter et al., "Filaggrin loss-of-function mutations are associated with enhanced expression of IL-1 cytokines in the stratum corneum of patients with atopic dermatitis and in a murine model of filaggrin deficiency," *Journal of Allergy and Clinical Immunology*, vol. 129, no. 4, pp. 1031.e1–1039.e1, 2012.
- [12] M. Fartasch, "Ultrastructure of the epidermal barrier after irritation," *Microscopy Research and Technique*, vol. 37, pp. 193–199, 1997.
- [13] M. Ponc and J. Kempenaar, "Use of human skin recombinants as an in vitro model for testing the irritation potential of cutaneous irritants," *Skin Pharmacology*, vol. 8, no. 1-2, pp. 49–59, 1995.
- [14] P. M. Elias, S. K. Ahn, M. Denda et al., "Modulations in epidermal calcium regulate the expression of differentiation-specific markers," *Journal of Investigative Dermatology*, vol. 119, no. 5, pp. 1128–1136, 2002.
- [15] M. Fartasch, E. Schnetz, and T. L. Diepgen, "Characterization of detergent-induced barrier alterations—effect of barrier cream on irritation," *Journal of Investigative Dermatology Symposium Proceedings*, vol. 3, no. 2, pp. 121–127, 1998.
- [16] K. P. Wilhelm, A. B. Cua, H. H. Wolff, and H. I. Maibach, "Surfactant-induced stratum corneum hydration in vivo: prediction of the irritation potential of anionic surfactants," *Journal of Investigative Dermatology*, vol. 101, no. 3, pp. 310–315, 1993.
- [17] K. R. Feingold, M. Schmuth, and P. M. Elias, "The regulation of permeability barrier homeostasis," *Journal of Investigative Dermatology*, vol. 127, no. 7, pp. 1574–1576, 2007.
- [18] L. C. Wood, P. M. Elias, C. Calhoun, J. C. Tsai, C. Grunfeld, and K. R. Feingold, "Barrier disruption stimulates interleukin-1 α expression and release from a pre-formed pool in murine epidermis," *Journal of Investigative Dermatology*, vol. 106, no. 3, pp. 397–403, 1996.
- [19] A. Grängsjö, A. Leijon-Kuligowski, H. Törmä, G. M. Roomans, and M. Lindberg, "Different pathways in irritant contact eczema? Early differences in the epidermal elemental content and expression of cytokines after application of 2 different irritants," *Contact Dermatitis*, vol. 35, no. 6, pp. 355–360, 1996.

- [20] S. Hoefakker, M. Caubo, E. H. M. Van't Erve et al., "In vivo cytokine profiles in allergic and irritant contact dermatitis," *Contact Dermatitis*, vol. 33, no. 4, pp. 258–266, 1995.
- [21] C. M. de Jongh, R. Lutter, M. M. Verberk, and S. Kezic, "Differential cytokine expression in skin after single and repeated irritation by sodium lauryl sulphate," *Experimental Dermatology*, vol. 16, no. 12, pp. 1032–1040, 2007.
- [22] I. Effendy, H. Löffler, and H. I. Maibach, "Epidermal cytokines in murine cutaneous irritant responses," *Journal of Applied Toxicology*, vol. 20, pp. 335–341, 2000.
- [23] J. N. W. N. Barker, R. S. Mitra, C. E. M. Griffiths, V. M. Dixit, and B. J. Nickoloff, "Keratinocytes as initiators of inflammation," *The Lancet*, vol. 337, no. 8735, pp. 211–214, 1991.
- [24] R. C. McKenzie and D. N. Sauder, "The role of keratinocyte cytokines in inflammation and immunity," *Journal of Investigative Dermatology*, vol. 95, no. 6, pp. 105S–107S, 1990.
- [25] H. Mizutani, R. Black, and T. S. Kupper, "Human keratinocytes produce but do not process pro-interleukin-1 (IL-1) β . Different strategies of IL-1 production and processing in monocytes and keratinocytes," *Journal of Clinical Investigation*, vol. 87, no. 3, pp. 1066–1071, 1991.
- [26] K. Zepter, A. Häffner, L. F. Soohoo et al., "Induction of biologically active IL-1 β -converting enzyme and mature IL-1 β in human keratinocytes by inflammatory and immunologic stimuli," *Journal of Immunology*, vol. 159, no. 12, pp. 6203–6208, 1997.
- [27] S. Kondo, S. Pastore, G. M. Shivji, R. C. McKenzie, and D. N. Sauder, "Characterization of epidermal cytokine profiles in sensitization and elicitation phases of allergic contact dermatitis as well as irritant contact dermatitis in mouse skin," *Lymphokine and Cytokine Research*, vol. 13, no. 6, pp. 367–375, 1994.
- [28] S. Lisby, K. M. Muller, C. V. Jongeneel, J. H. Saurat, and C. Hauser, "Nickel and skin irritants up-regulate tumor necrosis factor- α mRNA in keratinocytes by different but potentially synergistic mechanisms," *International Immunology*, vol. 7, no. 3, pp. 343–352, 1995.
- [29] E. Corsini, A. Terzoli, A. Bruccoleri, M. Marinovich, and C. L. Galli, "Induction of tumor necrosis factor- α in vivo by a skin irritant, tributyltin, through activation of transcription factors: its pharmacological modulation by anti-inflammatory drugs," *Journal of Investigative Dermatology*, vol. 108, no. 6, pp. 892–896, 1997.
- [30] P. F. Piguet, G. E. Grau, C. Hauser, and P. Vassalli, "Tumor necrosis factor is a critical mediator in hapten-induced irritant and contact hypersensitivity reactions," *Journal of Experimental Medicine*, vol. 173, no. 3, pp. 673–679, 1991.
- [31] R. W. Groves, M. H. Allen, E. L. Ross, J. N. W. N. Barker, and D. M. MacDonald, "Tumour necrosis factor alpha is pro-inflammatory in normal human skin and modulates cutaneous adhesion molecule expression," *The British Journal of Dermatology*, vol. 132, no. 3, pp. 345–352, 1995.
- [32] M. Detmar and C. E. Orfanos, "Tumor necrosis factor-alpha inhibits cell proliferation and induces class II antigens and cell adhesion molecules in cultured normal human keratinocytes in vitro," *Archives of Dermatological Research*, vol. 282, no. 4, pp. 238–245, 1990.
- [33] J. S. Pober and R. S. Cotran, "Cytokines and endothelial cell biology," *Physiological Reviews*, vol. 70, no. 2, pp. 427–451, 1990.
- [34] S. W. Spiekstra, M. J. Toebak, S. Sampat-Sardjoeersad et al., "Induction of cytokine (interleukin-1 α and tumor necrosis factor- α) and chemokine (CCL20, CCL27, and CXCL8) alarm signals after allergen and irritant exposure," *Experimental Dermatology*, vol. 14, no. 2, pp. 109–116, 2005.
- [35] T. Nakayama, R. Fujisawa, H. Yamada et al., "Inducible expression of a CC chemokine liver- and activation-regulated chemokine (LARC)/macrophage inflammatory protein (MIP)-3 α /CCL20 by epidermal keratinocytes and its role in atopic dermatitis," *International Immunology*, vol. 13, no. 1, pp. 95–103, 2001.
- [36] F. Liao, R. L. Rabin, C. S. Smith, G. Sharma, T. B. Nutman, and J. M. Farber, "CC-chemokine receptor 6 is expressed on diverse memory subsets of T cells and determines responsiveness to macrophage inflammatory protein 3 α ," *Journal of Immunology*, vol. 162, no. 1, pp. 186–194, 1999.
- [37] L. Landeck, M. Visser, S. Kezic, and S. M. John, "Impact of tumour necrosis factor- α polymorphisms on irritant contact dermatitis," *Contact Dermatitis*, vol. 66, no. 4, pp. 221–227, 2012.
- [38] L. Landeck, M. Visser, S. Kezic, and S. M. John, "IL1A-889 C/T gene polymorphism in irritant contact dermatitis," *Journal of the European Academy of Dermatology and Venereology*, vol. 27, no. 8, pp. 1040–1043, 2013.
- [39] C. J. Bae, S. B. Shim, S. W. Jee et al., "IL-6, VEGF, KC and RANTES are a major cause of a high irritant dermatitis to phthalic anhydride in c57BL/6 inbred mice," *Allergology International*, vol. 59, no. 4, pp. 389–397, 2010.
- [40] S. Palacio, D. Schmitt, and J. Viac, "Contact allergens and sodium lauryl sulphate upregulate vascular endothelial growth factor in normal keratinocytes," *The British Journal of Dermatology*, vol. 137, no. 4, pp. 540–544, 1997.
- [41] E. G. Lee, B. M. Mickle-Kawar, and R. M. Gallucci, "IL-6 deficiency exacerbates skin inflammation in a murine model of irritant dermatitis," *Journal of Immunotoxicology*, vol. 10, no. 2, pp. 192–200, 2013.
- [42] D. J. Berg, M. W. Leach, R. Kühn et al., "Interleukin 10 but not interleukin 4 is a natural suppressant of cutaneous inflammatory responses," *Journal of Experimental Medicine*, vol. 182, no. 1, pp. 99–108, 1995.
- [43] C. S. Newby, R. M. Barr, M. W. Greaves, and A. I. Mallet, "Cytokine release and cytotoxicity in human keratinocytes and fibroblasts induced by phenols and sodium dodecyl sulfate," *Journal of Investigative Dermatology*, vol. 115, no. 2, pp. 292–298, 2000.
- [44] K. Ouwehand, R. J. Scheper, T. D. de Gruijl, and S. Gibbs, "Epidermis-to-dermis migration of immature Langerhans cells upon topical irritant exposure is dependent on CCL2 and CCL5," *European Journal of Immunology*, vol. 40, no. 7, pp. 2026–2034, 2010.
- [45] Y. Kobayashi, M. Staquet, C. Dezutter-Dambuyant, and D. Schmitt, "Development of motility of Langerhans cell through extracellular matrix by in vitro hapten contact," *European Journal of Immunology*, vol. 24, no. 9, pp. 2254–2257, 1994.
- [46] K. Ouwehand, D. Oosterhoff, M. Breetveld, R. J. Scheper, T. D. de Gruijl, and S. Gibbs, "Irritant-induced migration of langerhans cells coincides with an IL-10-dependent switch to a macrophage-like phenotype," *Journal of Investigative Dermatology*, vol. 131, no. 2, pp. 418–425, 2011.
- [47] Y. Eberhard, S. Ortiz, A. Ruiz Lascano, R. Kuznitzky, and H. M. Serra, "Up-regulation of the chemokine CCL21 in the skin of subjects exposed to irritants," *BMC Immunology*, vol. 5, article 7, 2004.
- [48] H. Tang, C. Schlapbach, A. S. Hassan, D. Simon, and N. Yawalkar, "Characterization of dendritic cells and macrophages

- in irritant contact dermatitis,” *Journal of Dermatological Science*, vol. 57, no. 3, pp. 216–218, 2010.
- [49] L. Zhang and S. S. Tinkle, “Chemical activation of innate and specific immunity in contact dermatitis,” *Journal of Investigative Dermatology*, vol. 115, no. 2, pp. 168–176, 2000.
- [50] S. Meller, A. I. Lauerma, F. M. Kopp et al., “Chemokine responses distinguish chemical-induced allergic from irritant skin inflammation: memory T cells make the difference,” *Journal of Allergy and Clinical Immunology*, vol. 119, no. 6, pp. 1470–1480, 2007.
- [51] D. Pennino, K. Eyerich, C. Scarponi et al., “IL-17 amplifies human contact hypersensitivity by licensing hapten nonspecific Th1 cells to kill autologous keratinocytes,” *Journal of Immunology*, vol. 184, no. 9, pp. 4880–4888, 2010.
- [52] Y. Zhao, A. Balato, R. Fishelevich, A. Chapoval, D. L. Mann, and A. A. Gaspari, “Th17/Tc17 infiltration and associated cytokine gene expression in elicitation phase of allergic contact dermatitis,” *The British Journal of Dermatology*, vol. 161, no. 6, pp. 1301–1306, 2009.
- [53] A. J. van Beelen, M. B. M. Teunissen, M. L. Kapsenberg, and E. C. de Jong, “Interleukin-17 in inflammatory skin disorders,” *Current Opinion in Allergy and Clinical Immunology*, vol. 7, no. 5, pp. 374–381, 2007.
- [54] S. I. Ale and H. I. Maibach, “Irritant contact dermatitis versus allergic contact dermatitis,” in *Contact Dermatitis*, A. L. Chew and H. I. Maibach, Eds., pp. 11–22, Springer, Berlin, Germany, 2006.
- [55] M. J. Toebak, S. Gibbs, D. P. Bruynzeel, R. J. Scheper, and T. Rustemeyer, “Dendritic cells: biology of the skin,” *Contact Dermatitis*, vol. 60, no. 1, pp. 2–20, 2009.
- [56] J. P. McFadden and D. A. Basketter, “Contact allergy, irritancy and ‘danger,’” *Contact Dermatitis*, vol. 42, no. 3, pp. 123–127, 2000.
- [57] E. J. Villablanca and J. R. Mora, “A two-step model for Langerhans cell migration to skin-draining LN,” *European Journal of Immunology*, vol. 38, no. 11, pp. 2975–2980, 2008.
- [58] S. Aiba, A. Terunuma, H. Manome, and H. Tagami, “Dendritic cells differently respond to haptens and irritants by their production of cytokines and expression of co-stimulatory molecules,” *European Journal of Immunology*, vol. 27, no. 11, pp. 3031–3038, 1997.
- [59] M. J. Toebak, P. R. Pohlmann, S. C. Sampat-Sardjoepersad et al., “CXCL8 secretion by dendritic cells predicts contact allergens from irritants,” *Toxicology In Vitro*, vol. 20, no. 1, pp. 117–124, 2006.
- [60] L. A. Gildea, C. A. Ryan, L. M. Foertsch et al., “Identification of gene expression changes induced by chemical allergens in dendritic cells: opportunities for skin sensitization testing,” *Journal of Investigative Dermatology*, vol. 126, no. 8, pp. 1813–1822, 2006.