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Effector pathways during eczematous dermatitis: where inflammation meets cell death

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Abstract: During eczematous skin inflammation, the main constituents of the skin, keratinocytes (KC), play an important role in inducing and shaping the immunological response to environmental stimuli. This review focuses on the epidermal inflammation caused by keratinocyte-T cell interactions arising from a disturbed barrier function of the skin. In eczematous dermatitis, activated dermis- and epidermis-infiltrating T cells target KC for apoptosis. In turn, damaged KC respond by secreting inflammatory mediators, thus effecting further recruitment of immunocytes to inflamed skin. Further advances will come from identification of the immunoregulatory mechanisms involved in the pathogenesis of eczematous dermatitis. Potential therapeutic interventions are discussed.

Key words: allergic contact dermatitis – apoptosis – atopic dermatitis – keratinocyte – T cell

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Introduction

Eczematous dermatitis including atopic dermatitis (AD) and allergic contact dermatitis (ACD) are characterized by T cell infiltration into the dermis and epidermis. Although the effector pathways of activated T cells have been intensively studied, the active role of epidermal keratinocytes (KC) in induction and maintenance of eczematous dermatitis has been rather neglected. It has been suggested that apoptosis of KC induced by T cells and mediated by CD95 is a crucial event in the transition from activation of the immune system to the manifestation of eczematous dermatitis (1). However, during the past decade, it became obvious that KC are not only victims of unleashed T cell effector functions in disease, but rather actively participate and shape the epidermal response to effector T cells. Thus, the interplay of KC with immune effector cells merits a more detailed examination. Importantly, the molecular cross-talk between KC and T cells imposes KC as active players of the skin immune system. Upon activation, KC express a plethora of cytokines, chemokines and accessory receptors, which can either amplify or dampen immune responses of the innate and adaptive immunity. Accordingly, a dysregulation of inflammatory mediators or their cognate receptors in KC appear to be relevant for the pathogenesis of acute and chronic eczematous dermatitis.

Abbreviations: AD, atopic dermatitis; ACD, allergic contact dermatitis; CLA, cutaneous lymphocyte-associated antigen; ICAM, intercellular adhesion molecule; CCL, CC chemokine ligand; CCR, CC chemokine receptor; CXCL, CXC chemokine ligand; CXCR, CXC chemokine receptor.

Eczematous dermatitis: pattern of skin inflammation rather than specific disease

From a histological point of view, eczematous dermatitis is a rather uniform reaction pattern. Irrespective of the clinical type of eczema, the eczematous inflammation is characterized by suprabasal epidermal spongiosis and an inflammatory perivascular upper dermal infiltrate composed mainly of activated T cells. The clinical features are related to increased vascular blood flow (erythema), vascular permeability (edema), the migration of T cells into the dermal compartment (infiltration), epidermal spongiosis (vesiculation) and a release of pruritogenic mediators (itch). This pattern of skin inflammation can be induced and maintained by a variety of environmental or intrinsic factors (e.g. contact allergens, irritants, infective agents, atopy, filaggrin gene mutations) resulting in clinically more or less specific eczematous diseases. During inflammation, resident structural elements of the skin (e.g. KC, fibroblasts, endothelial cells) tightly interact with cells that are actively recruited from the blood in response to inflammatory stimuli. A complex interaction of numerous chemokines controls the recruitment of T cells from the blood vessels

and their migration into the dermal unit (2). Importantly, inflammation of the dermal-epidermal compartment is driven by the elaborated KC-T cell interactions by means of T cell-derived inflammatory cytokines, IFN-γ and a plethora of immunoregulatory mediators produced by KC. Thus, the local response of KC in concert with the reaction of endothelial cells, T cells, mast cells, eosinophils, fibroblasts and dendritic cells finally leads to the characteristic clinical and histological appearance of eczema. However, it should be kept in mind that the predominance of Th2 immune responses in acute stages of AD as compared to ACD has direct implications on the induction of IgE (auto-) antibodies to environmental or self-antigens (3). Of note, mouse models to study effector pathways of differential T cell populations or dermis-resident cells are widely used, but they are not very helpful to gain insights into the epidermal inflammation because the thin skin of mice e.g. lacks typical spongiosis formation (4,5).

It would be of great interest if the pathogenic steps in the development of eczema could be dissected on a molecular level. However, investigations into the differential (and unique) expression of inflammatory mediators in eczema are difficult to interpret as they have to incorporate a direct comparison between different types of eczema, stage of disease (acute versus chronic) or other skin diseases. Consequently, such studies have only been rarely performed in human skin. By applying DNA microarray techniques, several investigators demonstrated that the Th2-attractant CC chemokines CCL13/MCP-4, CCL18/PARC, CCL27/CTACK are increased in lesional skin of AD when compared to another inflammatory dermatosis, psoriasis (6–8). Bearing the dynamic course of AD and ACD in mind, it is therefore crucial to define the stage of disease (acute versus chronic) whenever effector mechanisms are evaluated. Especially, if such knowledge should be translated into specific therapeutic interventions, it may be essential to understand mediators which may be fundamentally different in the acute phase as compared to the chronic phase of eczematous dermatitis.

Depending on the stage of disease, it would be interesting to know if eczematous dermatitis share a common 'cytokine/chemokine signature', as it has been suggested for lichenoid dermatoses (e.g. lichen planus, lupus erythematodes). Wenzel et al. recently showed that upregulation of CXCR3 ligands (CXCL9/CXCL10) predominantly on KC is the common intersection of lichenoid dermatoses, thereby presumably facilitating the recruitment of $CXCR3^+$ and granzyme B^+ cytotoxic T cells to the basal epidermal layer where they attack basal $CXCL9^+$ or $CXCL10^+$ KC via the perforin/granzyme B pathway (9). Independently of the different etiopathogenetic backgrounds, lichenoid dermatoses converge at the early effector phase by type I IFN (α/β)-driven expression of this receptor-ligand pair as it has been proposed by the authors. Interestingly, the strong upregulation of CXCL9 distinguishes Lichen planus from AD or psoriasis, as it has been demonstrated by gene expression profiling of pooled skin biopsies (10). Intriguingly, the type II interferon IFN-γ is one of the big players in eczema, whereas in lichenoid dermatoses, it is a type I interferon (IFNα/IFNβ). Therefore, it is tempting to speculate that one or a few cytokines expressed early in disease might determine the outcome of inflammatory skin diseases. It will be challenging to track down such signatures of key cytokines/chemokines in the complex molecular mediator array during eczematous dermatitis.

Trouble ahead with a stimulating beverage: inflammatory cocktails that define crosstalks of immune effector cells with epidermal keratinocytes

As T cells constitute a large population of the cellular infiltrate in eczematous dermatitis, a dysregulated, cytokine-mediated response of the immune system appears to be an important pathogenetic factor (3). However, the early events in eczematous dermatitis leading to the recruitment of mainly effector $CD45RO^+$ T cells to the skin are poorly understood. One clue to this dilemma might be the capability of KC to produce cytokines after mechanical trauma and skin barrier disruption (11). Clinically, this scenario is well documented as the itch-scratch cycle, which might represent the starting point of primary skin inflammation. Mechanical trauma of the skin results in the induction of IL-1(α/β), TNF-α and GM-CSF (12). Furthermore, contact allergens and irritants can directly induce inflammatory activation of KC resulting in expression of ICAM-1, IL-8, TNF-α and CCL2/MCP-1. Importantly, changes in these expression pattern within the epidermis clearly precede the infiltration of T cells and monocytes (2,13). Recently, it has been suggested that KC might provide a link between innate and adaptive immunity through activation of the inflammasome, an intracellular signalling platform for the activation of proinflammatory caspases, which in turn lead to the release of proinflammatory cytokines such as IL-1β and IL-18. Similar to Toll-like receptors, inflammasomes are players of the innate immunity and sense for danger signals (14), e.g. microbial products (e.g. derived from *Staphylococcus aureus*), ATP, uric acid crystals or cellular stress (15). Work by Watanabe et al. demonstrated that the contact allergen trinitro-chlorobenzene can induce inflammasome-dependent activation of IL-1β and IL-18 in KC and it has been suggested that in this setting, the inflammasome initiates proinflammatory signals promoting T cell priming (16). If mechanical trauma-mediated activation of IL1-β (12) occurs in an inflammasome-dependent fashion has to be clarified in future studies.

A new light on the role of the proinflammatory (mainly by IFN-γ induction in T cells) IL-18 in the development of AD in humans was shed by Novak et al. who demonstrated that the IL-18 secretion of peripheral blood mononuclear cells (PBMC) of AD affected patients stimulated with staphylococcal enterotoxin B was significantly higher as compared with healthy control subjects (17). *In vivo* exacerbation of disease was associated with an increase in serum IL-18. As single nucleotide polymorphisms in exon 1 and the promoter region of the IL-18 gene were associated with an AD phenotype, the authors suggested that a functional dysregulation of the IL-18 gene transcription might contribute to the development of AD.

The recent discovery that the IL-17-producing $CD4^+$ T cells (Th17 cells) can be found in the epidermis and dermal infiltrate of AD merits a role for this newly recognized T cell lineage in the pathogenesis of this disease (18,19). Most notably, IL-17 is involved in inducing and mediating proinflammatory responses through upregulation of GM-CSF, IL-8, TNFα and the chemokine CXCL10 by KC (18) and also resident cells like fibroblasts (20). High levels of IL-17 were found in acute but not chronic lesions of AD suggesting that Th17 cells may act as an amplifier of the elicitation phase of AD. Interestingly, the stimulation of Th2/IL-17 or Th0/IL-17 T cell clones derived from atopy patch tests to *Dermatophagoides pteronyssinus* (Der) with the superantigen staphylococcal entertoxin B (SEB) and Der p1 strongly enhanced the secretion of IFN-γ, and especially IL-17, as compared to stimulation with antigen alone (21). These findings suggest that depending on the microenvironment, Th17 cells have the capacity to enhance skin inflammation by acting on KC to produce further proinflammatory cytokines such as GM-CSF, IL-8 and TNFα. However, further studies are needed to clarify the role of Th17 cells in the pathogenesis of AD, especially the phase of the disease during which these cells might play a role. During inflammation, leucocytes follow chemotactic gradients to attach to activated endothelial cells resulting in leucocyte penetration of the subendothelial matrix and migration to areas of tissue damage (22). This process involves coordinated signalling events mediated by proinflammatory cytokines and chemokines, and sequential interactions with multiple adhesion molecules including selectins and their ligands, integrins. Secretion of IL-1 and TNF-α by KC results in activation of dermal endothelial cells and production of surface leucocyte adhesion ligands ICAM-1, E-Selectin as well as VCAM-1, consequently leading to the recruitment and diapedesis of predominantly skin homing cutaneous lymphocyte-associated antigen $(CLA)^+/CD45RO^+$ T cells from the blood circulation (22). Concomitant secretion of IL-8 and IL-1 by KC promotes directional T cell migration along a chemotactic gradient to the epidermis, where T cells expressing LFA-1 adhere to KC via interactions with the LFA-1 ligand, ICAM-1. *In vitro* T cell adherence to KC is LFA-1/ICAM-1-dependent (23,24) and *in vivo* $ICAM\text{-}1^+$ KC colocalize with $LFA\text{-}1^+$ T cells (25), indicating an important role of this receptor/ligand pair for epidermis infiltration of activated T cells.

The initial proinflammatory response by KC causes additional synthesis of further KC-derived chemokines like CCL27/CTACK. CCL27/CTACK is a skin-specific chemokine exclusively expressed in epidermal KC under homeostatic conditions and inducible by proinflammatory mediators, such as TNF-α and IL-1β (26). CCL27 preferentially recruits $CCR10^+$ skin homing memory T cells to inflamed skin. The relevance of CCL27-CCR10 interactions in attracting $CD45RO^+$ T cells in eczematous inflammation was demonstrated in mouse models mimicking ACD and AD (27). In these models, neutralization of CCL27 impaired inflammatory skin responses.

The interleukin-7-like thymic stromal lymphopoietin (TSLP) is mainly expressed by barrier epithelial cells, especially KC from patients with AD, and has an important role in instructing dendritic cells to induce a Th2 response following allergen contact (28). TLSP-activated myeloid DC prime Th2 cells to produce IL-4, IL-5, IL-13 and TNFα, but little or no IL-10 or IFN-γ (28). In addition, stimulation of DC with TSLP results in release of large amounts of IL-8 and eotaxin-2, which attract neutrophils and eosinophils, as well as CCL17/TARC and CCL22/MDC, which attract TH2 cells (29). The expression of TSLP is controlled by synergism of proinflammatory and Th2 cytokines such as TNFα and IL-4 (30). Using a transgenic mouse model of allergic skin inflammation elicited by repeated epicutaneous OVA appliance, He et al. showed that TSLP plays a role in the effector phase of Th2-dominated allergic skin inflammation by enhancing local Th2 cytokine production by skin-infiltrating antigen-specific $CD4^+$ T cells (31). Taking these findings together, TSLP might act as an amplifier of proinflammatory responses in the effector, but not in the initial phase of AD.

IFN-γ is a key cytokine secreted by activated $CLA^+/CD45RO^+$ T cells recruited to the site of inflammation and represents one of the strongest activators of KC, which in turn upregulate surface molecules (e.g. ICAM-1, MHC class II, CD95, CD40), chemokines (e.g. CCL2/MCP-1, CCL22/MDC, CXCR3 ligands, CCL3/MIP-1α, CCL4/MIP-1β, CCL18/PARC, CCL5/RANTES, CXCL8/IL-8, CXCL10/IFN-γ inducible protein-10 (IP-10) and cytokines (e.g. IL-1, IL-18, IL-6, IL-15, TGF-β) (32,33). Of these molecules, CXCL10/IP-10, CCL2/MCP-1 and ICAM-1 are highly inducible by IFN-γ in KC (1,2). Interestingly, upregulation of CD95 by IFN-γ exerts a dual action: On one hand, localized sensitization to CD95-mediated cell death executed by invading T cells through membrane bound and secreted CD95L, and on the other hand, conferring

apoptosis resistance through CD95L-induced secretion of EGF ligands with paracrine anti-apoptotic effects on surrounding KC (as outlined below).

Finally, in the course of epidermal inflammation, KC might present antigen to T cells. Although KC that can act as non-professional APC are still controversially discussed, Black et al. demonstrated that KC are able to process endogenous as well as exogenous antigens and induce rapid effector functions thereby perpetuating cutaneous CD4 and CD8 memory T cell responses (34). Importantly, there is a large body of evidence that abnormal colonization of *S. aureus* contributes to the pathogenesis of AD. In particular, *S. aureus* present on the skin of atopic indiciduals is more likely to express superantigens such as staphylococcal enterotoxins A and B (SEA, SEB) as well as staphylococcal toxic shock syndrome toxin-1 which in turn contribute to the inflammation. First, they cause (like IFN-γ and TNFα) upregulation of MHC class II molecules on KC and secondly crosslink MHC class II/TCR Vβ chains thereby promoting antigen-independent activation, induction and expansion of CLA^+ T cells further fostering proinflammatory responses (35–37). In addition, it has been shown that SEB can facilitate KC presentation of allergen to $CD4^+$ T cells thereby enhancing allergen-specific Th2 responses (38).

As outlined above, KC thus contribute to the vigorous immigration of T cells by expression of primary proinflammatory cytokines, highlighting that rather unspecific non-immunological mechanisms precede and corroborate the widely studied antigen-specific mechanisms during the elicitation phase of eczematous dermatitis.

Peace maker? Apoptosis resistance and sensitivity of epidermal keratinocytes

One important event during the effector phase of eczematous dermatitis might be the regulation of KC cell death. T cell-mediated CD95-induced KC apoptosis has been postulated as an important pathogenetic event in spongiosis formation, the histopathological hallmark of acute eczema (1). In this context, apoptosis might severely influence the magnitude and spread of the inflammation from the space of T cell invasion by several mechanisms. The most obvious reason could be that efficient reduction of KC surrounding the epidermis-located inflammatory cells is critical, as proposed (39). Indeed, apoptotic KC are numerously found in biopsies of acute AD or ACD as demonstrated *in situ* by TUNEL assay, Hoechst stain and processed caspase-3 (p17) (1,40–42). Thus, cell death of epidermal KC contributes during the effector phase of contact eczema to the quantitative and qualitative responses in the skin and its termination. An alternative hypothesis might be that apoptosis of KC is crucial to keep the skin inflammation restricted to the region of contact with the allergen or is required for a predominant homing of antigen-specific lymphocytes to the site of allergen exposure, whereas the distribution of antigen-specific T cells to sites without allergen contact might be regulated differently.

In the context of T cell-KC crosstalk in the skin, $CD8^+$ T cells may either utilize the intrinsic (mitochondrial) apoptotic signalling pathway that is activated by perforin-dependent granzyme-mediated death signals (43) or the extrinsic cell death pathway (44). Perforin-granzyme B-mediated cell death signals might be critical for cell death in lichen planus, dominated by type I IFNs and the occurrence of a predominant $CD8^+$ interface dermatitis (9), whereas the contribution of these cell death signals to eczematous dermatitis remains unclear to date. Death receptor (DR) signals are crucial for apoptosis of KC in eczematous skin, as shown for CD95 and its ligand. These (or likely other death ligands) are dominantly expressed on activated $CD45RO^+$ T cells (1,41). However, the presence of receptor or ligand is not sufficient to induce DR-mediated apoptosis (45–47). Notably, DR as well as procaspases are widely expressed in the skin (48,49), but 'accidental' cell death by caspase activation is blocked by inhibitors of effector caspases, e.g. inhibitor-of-apoptosis proteins [IAP's, (50,51)], or inhibitors of initiator caspases, e.g. exemplified by cellular FLICE-inhibitory proteins [cFLIP, for review see (52,53)]. cFLIP proteins can be considered as intrinsic dominant-negative DR inhibitory proteins that keep the activation of caspase-8 in check. Adding to the complexity of the pathophysiology and the function of DR, it is now accepted that several of these surface receptors also transmit non-apoptotic signals, e.g. through NF-κB or mitogen-activated protein kinases (MAPK) activation, to the DR-expressing cell [for review, see (46)]. Interestingly, cFLIP is crucial for the blockade of DR-mediated cell death by CD95 and TRAIL-R, but does not block TNF-R1-mediated proinflammatory signals (54). Importantly, DR-induced non-apoptotic signals are not likely to be needed to modulate apoptosis induction but rather to initiate cellular inflammatory responses. Thus, DRs may shape the quality and quantity of the cytokine cocktail produced during the effector phase of ACD (55,56). These functions may have important and distinct pathophysiological consequences during different stages of the effector phase of eczematous dermatitis that have not yet been elucidated. Another aspect in this context might be that the cellular environment in eczema itself impacts the death ligand sensitivity of skin KC. For example, IFNs (α and γ) are able to increase the sensitivity to DR-mediated apoptosis (57). These important cytokines, produced either by activated T cells (IFN) or fibroblasts and resident plasmacytoid DCs, might commence the apoptosis sensitization process of epidermal KC and may thereby critically influence DR sensitivity in the skin during the intricate interplay between KC and skin-infiltrating

T-cells (39). Thus, the cellular components of the dermis that have to be passed by T cells transmigrating the vessels as well as the matrix components on their way to the epidermis might lead to increased DR expression, as shown for CD95 in response to IFN-γ (58–60), or by modification of the dynamics of caspase activation at the DR complex (DISC) (57). Importantly, activation of caspases is not identical to cell death, thereby marking caspases as important molecules for non-apoptotic signalling initiated by KC. Thus non-apoptotic signals generated by DR ligation by CD95L (61) or other death ligands could prove critical in eczema. Of note, most of these DR-activated signals are induced rapidly after CD95L stimulation, with the notable exception of IL-1β (61). Thus, the stoichiometry of the intracellular proteins that are available for recruitment to and assembly of the DISC, such as FADD, cFLIP, caspase-8, or RIP (62) may modulate not only apoptosis but also proinflammatory signals generated by DL. For example, cFLIP efficiently blocks DR-mediated NF-κB activation induced by the DL TRAIL (62) or CD95L in HaCaT KC (55,63). Although there is no knowledge about the regulation of cFLIP by IFNs in the skin, this might represent an interesting area of research for the future.

Another signalling event crucial to maintain apoptosis resistance in skin KC is the highly expressed EGFR-EGFR ligand (EGF-RL) system (64). CD95L rapidly induces EGF-R ligands in a caspase-dependent manner (65). In turn, EGF itself is able to confer resistance to apoptosis induction by activation of the PI3K/Akt signalling pathway that in turn regulates cFLIP levels (66). There is sufficient evidence to suggest that DL may activate by themselves antiapoptotic as well as proliferative signalling pathways that secure DL resistance of the surrounding KC. In this context, it will be interesting to determine why caspase inhibitors such as zVAD-fmk block cell death, but not proinflammatory signals elicited by DR and why the intracellular caspase inhibitor cFLIP also blocks proinflammatory signals (62,63). Results of such studies might prove extremely useful for the understanding if the blockade of caspases will be beneficial or rather detrimental for the development of eczematous dermatitis. As apoptosis is required for the EGF-R ligand secretion, apoptosis resistance of DR in turn might counter-regulate this secretion. If DR are still able to signal for proinflammatory pathways in response to TRAIL (56) or CD95L, as suggested by previous studies (55), such a szenario might result in increased (and potentially detrimental) inflammation whenever cell death does not occur. Taking together these findings, a shift in the balance between pro- and anti-apoptotic proteins may be sufficient to modulate the outcome of DR triggering exerted by skin-homing T cells (Fig. 1). As cFLIP is strongly expressed in the basal layer of the interfollicular epidermis (41), this might be one important argument for the occurrence of KC apoptosis only in the suprabasal layers during eczematous dermatitis (41).

So what? Potential therapeutic implications for the understanding of effector pathways

One major problem of AD is that it often cannot be adequately controlled with topical agents and the continuous use of several systemic therapies for AD is limited by end-organ toxicities. Therefore, a safe and effective topical or systemic therapy for patients with recalcitrant eczematous dermatitis, especially AD, is desirable. Remarkably, most of the few targeted therapeutic approaches were backed up on the clinical efficacy of antipsoriatic biological agents, and largely address blockade of T cell effector functions. The most obvious way to disturb the T cell-KC crosstalk is the disturbance of T cell invasion into the skin, as it has been exemplified by the use of efalizumab, a LFA-1 neutralizing monoclonal antibody. In a prospective open trial pilot study, Takiguchi et al. studied 10 patients with severe AD, of which 6 demonstrated at least a 50% improvement of the EASI score within 12 weeks of treatment (67). However, as a result of three cases of progressive multifocal leucencephalopathy in the course of long-term treatment of psoriasis, this mAb was suspended from marketing in early 2009. Also, TNF-α blockade showed a more or less effective response (68–70). Lastly, alefacept, a fully human LFA-3/IgG1 fusion protein with a dual mechanism of action inhibiting T-cell activation as well as selectively reducing memory T cells, was used in an open-label study. Here, only two out of the nine patients with AD responded to treatment (71). Although it is clearly premature to draw any conclusions from these studies, it somewhat becomes obvious that simply blocking T cell effector functions is not the 'holy grail' for the treatment of AD. Rather, it takes 'two to tango', most likely KC as well as T cells to induce skin pathology in AD.

In line with this idea, retinoids harbour an anti-inflammatory and immunomodulatory mechanism of action and affect both KC and T cells. For example, the panagonist of retinoic acid receptors A (RAR) and X (RXR), alitretinoin, directly affects cytokine production in KC and down-regulates leucocyte activity (72–74). Furthermore, it controls KC differentiation and therefore might be essential to reconstitute the perturbed barrier function of the skin in eczematous dermatitis, as it has been shown in chronic hand eczema (75), which often display a mixture of ACD and AD (76). However, the pharmacological action of RAR and RXR agonists leads almost certainly to augmentation of skin dryness (a key pathogenic factor in AD) and further disturbs epidermal barrier function. Thus, it remains to be determined in future experimental studies how the inter-

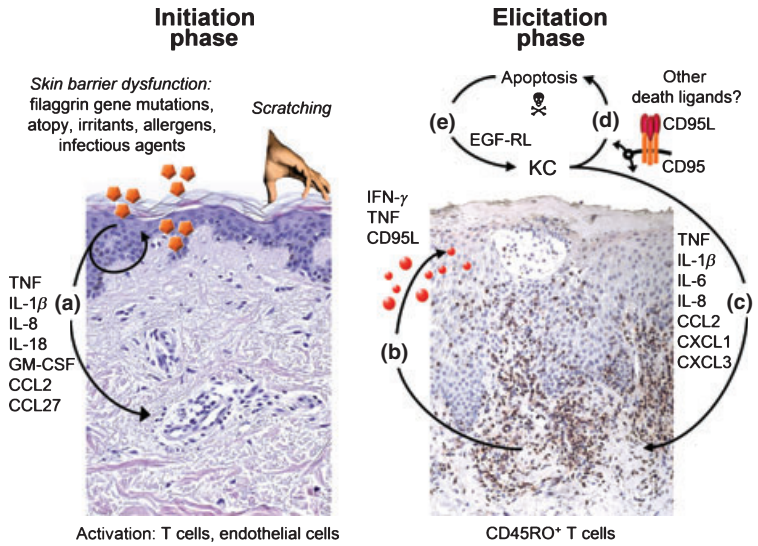

Figure 1. Model of sequential keratinocyte-T cell crosstalk in the progression of eczematous inflammation. (a) A crucial point to set off epidermal inflammation is the disturbance of skin barrier function by filaggrin gene mutations in AD, atopy, irritants, allergens or microbial colonization. In parallel, scratching causes keratinocyte (KC) activation and additionally leads to skin barrier disruption perpetuating skin penetration of environmental agents. As a consequence, these factors trigger a non-immunological cutaneous inflammatory response by directly inducing epidermal KC to secrete proinflammatory cytokines such as TNF-α, IL-1β, IL-8, IL-18, GM-CSF or via a potential auto-/paracrine feed-back loop CCL27/CTACK. Most of these cytokines facilitate the immigration of skin-selective T cells into the dermis by activation of endothelial cells. (b) During the elicitation phase, CD45RO$^+$ effector T cells secrete TNF-α, IFN-γ. In the process of directed migration, activated T cells cross the basal membrane and reach the epidermis where they closely interact with KC via ICAM-1/LFA-1 interactions. (c) Epidermal KC may act as amplifiers through non-apoptotic death receptor-triggered NF-κB- and MAPK-signalling enhancing pro-inflammatory cytokine responses that may attract further cellular infiltration. (d) As worst-case scenario, single KC undergoing CD95-mediated apoptosis spotlighting the pro-apoptotic response in eczema, which may act as an anti-inflammatory break simply via elimination of KC to restrict uncontrolled inflammation. Therefore, resistance or susceptibility of epidermal KC to CD95-mediated apoptosis might play a decisive role in amplifying [by secretion of pro-inflammatory cytokines, (c)] or damping further immune responses [by apoptosis, (d)]. In this concept, the potential role of other death ligands remains to be determined. (e) Upon apoptosis, KC secrete EGF-R ligands (EGF-RL), which mediate further inflammatory responses (e.g. through induction of IL-8) and potentially support apoptosis resistance of surrounding KC.

play between KC and immunocytes are differentially affected by different RAR and/or RXR agonists to get an insight into potential clinical effectiveness for AD. Nonetheless, it will be interesting to investigate the functional outcome of RAR/RXR agonists during the effector phase of eczematous dermatitis.

Although inhibition of caspases and thus blocking cell death in the epidermis is a compelling idea, doubts about such a therapeutic approach are warranted. Inhibition of caspases will most likely block apoptosis in the skin [as has been demonstrated in a human skin equivalent model (55)]. This might result in repression of spongiosis, but caution is warranted with respect to other signals activated by DR in the presence of such caspase inhibitors (39,55,56). It cannot be excluded that caspase inhibition might result in increased inflammation because DR-activated KC are no longer eliminated from the skin as a source of proinflammatory cytokines. More likely, a potential therapeutic effect of caspase inhibitors could be exerted by the dual inhibition of spongiosis together with the inhibition of inflammatory caspases such as caspase-1. Caspase-1 and other inflammatory caspases are activated at the inflammasome and are critical for the maturation of IL-1β, IL-18 and IL-33. For example, inflammasome-activated IL-33 may recruit additional cellular components of AD/ACD such as basophils as well as eosinophils to the site of antigen challenge (16,77). This more recently identified signalling platform for cytokine maturation in the skin may be of major relevance for the development of the initiation as well as effector phase of contact eczema (16,78,79). Importantly, in particular the family of NOD-like receptors is quite different between mouse and man (15). Thus caution is warranted to translate knowledge gained in mice to man with respect to activation and regulation of inflammasomes in the skin. Nonetheless, the data available to date establish that inhibitors of IL-1β such as IL-1 receptor antagonists, readily available as therapeutic substances because of its success in other IL-1-controlled diseases (80), novel antibodies against IL-1 forms currently tested in early clinical studies, or direct chemical inhibitors of inflammasome formation that interfere with nucleotide binding for the NOD-like receptors (81) might prove extremely useful for the treatment of acute eczema.

Ultimately, the translation of basic scientific knowledge gained over the past decade to therapeutic modalities for eczema patients may also require the development of novel model systems to study such therapeutic approaches in human skin in more detail. Such an approach has been successfully applied to studies for the understanding of the pathogenesis of psoriasis (82).

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