

Review

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Fas Receptor: An Overview

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ABSTRACT

The FAS receptor (FasR), also known as apoptosis antigen 1 (APO-1 or APT), cluster of differentiation 95 (CD95) or tumor necrosis factor receptor superfamily 6 (TNFRSF6) is a protein that in humans is encoded by the FAS gene. Engagement of the cell death surface receptor Fas by Fas ligand (FasL) results in apoptotic cell death, mediated by caspase activation. Cell death mediated *via* Fas/FasL interaction is important for homeostasis of different cell types. In this review, we want to highlight the role of Fas receptor in different dermatologic disorders. This would definitely help our understanding of its important role in dermatology that can open a new era in using anti-Fas biologic therapy in the future management of such disorders.

KEYWORDS: Apoptosis; FasL; Fas; TNF- α ; Death receptor.

ABBREVIATIONS: TNFR: Tumor Necrosis Factor Receptor; TNFRSF 6: Tumor Necrosis Factor Superfamily; AIF: Apoptosis Inducing Factor; IAP: Inhibitors of Apoptosis.

INTRODUCTION

Fas [APO-1/CD95/tumor necrosis factor superfamily 6 (TNFRSF6)/APT-1] is a transmembrane receptor expressed in particular in brain, heart, kidney, liver, pancreas, thymus and lymphoid tissues. It belongs to the death receptor family, a subgroup of the Tumor Necrosis Factor (TNF)/Nerve Growth Factor (NGF) receptor superfamily,^{1,2} and acts as the target of cell death-inducing antibodies.³

These cell surface cytokine receptors are able to initiate an apoptotic signaling cascade after binding a group of structurally related ligands or specific antibodies. In addition to its apoptotic function, it has other cellular responses including migration, invasion, inflammation, and proliferation. The members of this family are type I transmembrane proteins with a C-terminal intracellular tail, a membrane-spanning region, and an extracellular N-terminal domain rich in cysteine. Through interaction with the N-terminal domain, the receptors bind their cognate ligands (called death ligands).⁴ Although soluble forms of the receptor also exist, whose functions are still largely unknown, the membrane-bound form is largely predominant and highly biologically active.⁵

Fas is one of the members of the TNFR superfamily, currently comprising 29 receptors that are mirrored by only 19 ligands, representing the cognate TNF ligand superfamily. This already indicates that a single ligand might be capable to bind to more than one receptor and/or that there still exist orphan receptors.⁶

Activation of CD95-associated intracellular signaling pathways is not a simple consequence of ligand binding but is the fine-tuned result of a complex interplay of various molecular mechanisms that eventually determine the strength and quality of the CD95 response.³

In order to avoid unnecessary activation of the apoptotic pathway, Fas expression and localization are tightly regulated through a variety of mechanisms. The minimum amount of Fas is expressed on the plasma membrane in unstimulated cells (whereas the majority of the

receptor localizes in the cytosol, in particular, in the golgi complex and the trans-golgi network).⁷ Then, after a proapoptotic stimulus, Fas-containing vesicles translocate to the cell surface, increasing Fas expression on the plasma membrane and initiating the apoptotic signal. This mechanism provides an effective tool to regulate the plasma membrane density of the death receptor, and avoid its spontaneous activation.^{7,8}

Fas can also be modulated at a post-translational level, by glycosylation of the receptor,⁹ as well as at the transcriptional level, by direct regulation of Fas expression. A composite binding site for the transcription factor nuclear factor kappa B (NF- κ B) is located in the Fas gene promoter,¹⁰ and a p53-responsive element has been identified within the first intron of the Fas gene, which co-operates with three sequences in the promoter to up-regulate Fas receptor expression.¹¹

In eczema, spongiosis is predominantly located in suprabasal epidermal layers, suggesting an anti-apoptotic mechanism protecting basal KCs. CD95 is slightly up-regulated on KCs throughout all epidermal layers in eczematous dermatitis as compared with healthy skin.^{12,13} Thus, differential CD95 expression may basically account for the increased susceptibility of KCs to CD95-mediated apoptosis in eczema, but does not explain the apoptosis resistance of basal KCs. The differential expression of pro- and anti-apoptotic factors, which may influence the susceptibility to CD95-mediated apoptosis, might provide an

explanation for the restriction of spongiosis to suprabasal epidermal layers.¹⁴

MECHANISM

In non-stimulated cells Fas pre-aggregates in the form of complexes due to its amino-terminal pre-ligand-binding assembly domain.^{10,15}

Fas death receptor is physiologically activated through binding to its cognate ligand, Fas ligand (FasL). Fas/FasL interaction induces oligomerization and aggregation of Fas receptor, leading eventually to apoptosis after protein-protein interactions with adaptor and effector proteins.¹⁶ Binding of CD95 or agonistic antibodies to CD95 leads to formation of a receptor complex at the cellular membrane, which was named death-inducing signal complex (DISC).¹⁷

The DISC consists of oligomerized receptors, the death domain (DD)-containing adaptor molecule fas-associated death domain/mediator of receptor-induced toxicity (FADD/MORT1), procaspase-8 [FADD-like interleukin-1 beta-converting enzyme (FLICE), MACHa, Mch5], procaspase-10 and the cellular Flice like inhibitory protein (c-FLIP) (Figure 1). The DD of the receptor interacts with the DD of FADD, whereas the death effector domain (DED) of FADD interacts with the N-terminal tandem DEDs of procaspase-8, procaspase-10 and c-FLIP. As a result of

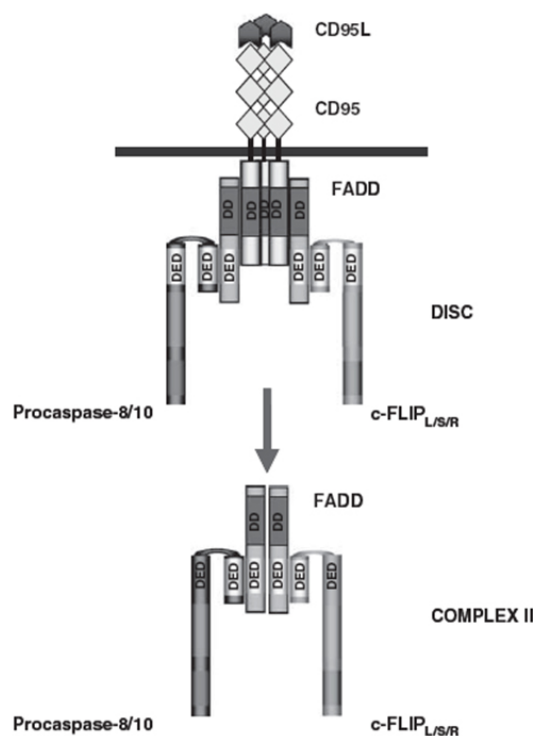


Figure 1: The CD95 DISC and complex II. The DISC consists of CD95, FADD, procaspase-8/procaspase-10 and c-FLIP. Complex II comprises FADD, procaspase-8/10 and c-FLIP. The interactions between the molecules at the DISC and complex II are based on homotypic contacts. The DD of CD95 interacts with the DD of FADD while the DED of FADD interacts with the N-terminal tandem DEDs of procaspase-8, procaspase-10 and c-FLIP.¹⁸

DISC formation procaspase-8 is activated at the DISC resulting in the formation of the active caspase-8, which leads to apoptosis.¹⁸

While FADD binds directly to the DD of Fas by its own C-terminal DD, procaspase-8 is indirectly recruited to Fas *via* FADD, which interacts *via* its N-terminal DED with the corresponding structure in procaspase-8. This FADD-mediated recruitment into the DISC allows the transient formation of enzymatically active procaspase-8 dimers that convert by autoproteolytic processing to mature active caspases-8 heterotetramers, mature caspase-8 is released from the DISC and, dependent on the cell type, can trigger the execution phase of apoptosis by two pathways, the extrinsic and the intrinsic pathway.¹⁹

Extrinsic pathway of apoptosis is induced by the signal molecules-known as ligands—which are released by other cells, and which bind to the transmembrane death receptors of the target cell. For example, the immune system's natural killer cells possess the FasL on their surface: the binding of the FasL to Fas receptors (Fas-R) (a death receptor) on various target cells will trigger the aggregation of multiple receptors on the surface of that target cell.²⁰ The aggregation of these receptors then leads to the recruitment of an adapter protein, known as FADD, on the cytoplasmic side of the receptors. FADD, in turn, recruits caspase-8 (an initiator protein), forming the DISC.²¹

The intrinsic pathway is triggered by cellular stress—specifically, mitochondrial stress caused by various factors, such as Deoxy Ribonucleic Acid (DNA) damage. The stress signal will cause the pro-apoptotic proteins found in the cytoplasm—BAX (pro-apoptotic, cytoplasmic protein) and BID—to bind to the outer membrane of the mitochondria and signal the release of the internal mitochondrial content. However, the signal of BAX and BID is not enough to trigger a full release of the mitochondrial content: BAK, a pro-apoptotic protein found in the

mitochondria, is also needed to fully promote the mitochondrial release; it is important to note that the mitochondrial content also includes cytochrome C. (Figure 2). Besides cytochrome C, the mitochondrial content released also contains the apoptosis-inducing factor (AIF) which facilitates DNA fragmentation, preventing the activity of the inhibitors of apoptosis (IAP).^{22,23}

The ligation of Fas by FasL causes the activation of target cell enzymes to degrade target cell nuclear DNA with concomitant fragmentation of the target cell nucleus, leading to programmed cell death. When FasL binds Fas, Fas trimerizes and activates its “death” domain that interacts with the “death” domains of several cytosolic proteins including FADD. Activation of FADD triggers the activation of a series of cysteine proteases known as caspases, resulting in apoptosis of the cell with the consequent morphological changes (reduction of cell volume, plasma membrane blebbing, condensation of chromatin, and fragmentation of DNA).^{2,24,25}

Phosphatidylserine, normally found on the cytosolic surface of plasma membranes, is redistributed during the process of apoptosis to the EC surface. Phagocytic cells recognize this aberrant placement and remove the dying cells without the induction of inflammation. Cell removal is followed by a reset of the activated T-lymphocytes to initiate another Fas/FasL interaction.^{2,26}

FAS LIGAND (FasL)

FasL (CD178/TNFRSF6/APTILG1) is a trimeric type II transmembrane protein that plays an important immune-regulatory role in limiting the host immune response.²⁷

The human FasL gene was mapped on chromosome 1q23 by *in situ* hybridization. The FasL gene consists of approximately 8.0 kb and is split into four exons.²⁸

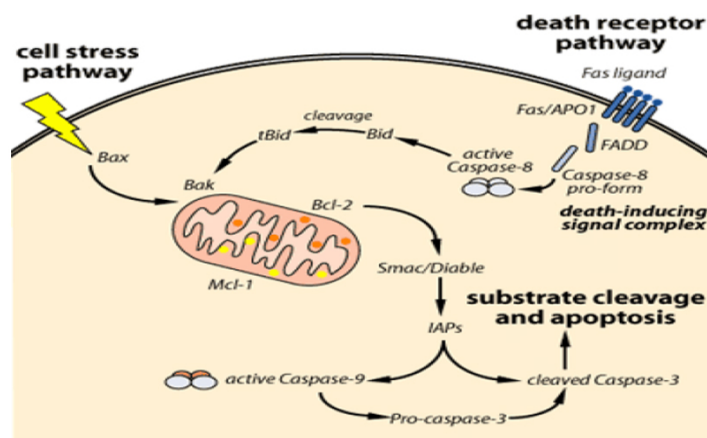


Figure 2: The intrinsic and extrinsic pathways leading to apoptosis.²¹

FasL is predominantly expressed on activated T-lymphocytes and natural killer cells but also at immune privileged sites. Similar to many other members of the TNF ligand superfamily, FasL can be cleaved by metalloproteinases in its EC domain to release the soluble trimetric ligand.²⁷ Both forms are capable to bind to Fas, but only membrane bound FasL is efficient in induction of cytotoxicity.²⁹

As soluble FasL competes with the membrane-bound counterpart, however, it can act even as an antagonist preventing apoptosis induction by the membrane integrated form of the ligand.^{30,27} On the other hand, soluble FasL binds effectively to fibronectin of the EC matrix, which results in retention of the molecule and an enhanced capacity to induce apoptosis.³¹ Besides its role in the blockage of apoptosis the soluble form of FasL has been shown to function as a strong chemo-attractant, and to enhance neutrophil and phagocyte migration to inflammatory sites (Figure 3).^{32,33}

Binding of membrane FasL to Fas triggers the re-organization of these complexes into signaling competent ligand-receptor aggregates. These aggregates are capable to interact with cytoplasmic signaling molecules. In sensitive cells this "active" Fas complex inducing apoptosis has been named DISC.³⁴

ROLE OF FAS

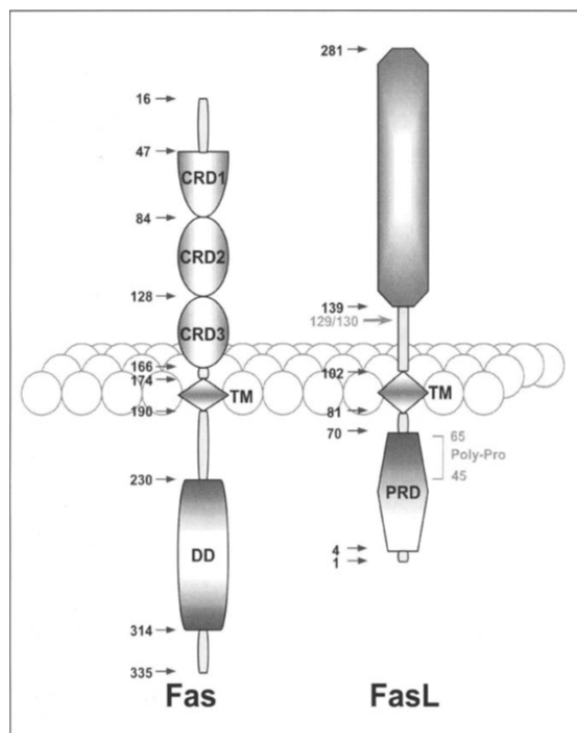
Fas/FasL: Key Role in Autoimmunity

Normally, in order to eliminate auto-reactive T-cells (mature T-lymphocytes that recognize self-antigens), interaction between auto-reactive T-cell Fas and activated T-lymphocytes Fas L induces apoptosis of the auto reactive T-cells. Inadequate removal of self-reactive T-lymphocytes permits the production of pathogenic auto-antibodies that characterize autoimmune diseases.³⁵

This negative regulation of T-cells contributes to the elimination of T-lymphocyte-activated auto-reactive B-cells, in the absence of presentation of the auto-antigen by the auto-reactive T-cell.²⁴

By virtue of elimination of these cells, the immune system remains safe and effective. Thus, normal Fas/FasL function results in normal lymphocyte homeostasis and controlled auto-reactivity. An alteration in Fas/FasL structure results in impaired immune tolerance and in uncontrolled lympho-proliferation.^{36,37}

Fas-mediated apoptosis plays a critical role in the removal of mature auto-reactive B- and T- lymphocytes as well



Small arrows indicate amino acid numbers, the larger arrow the putative metalloproteinase cleavage site.

Figure 3: Schematic representation of Fas and FasL. Fas is a type I and FasL a type II transmembrane protein. The upper parts of both molecules represent the extracellular domains. CRD=cysteine rich domain; TM=transmembrane domain; DD=death domain; PRD=proline rich domain.

as in the elimination of infected or malignant cells.²⁴ A dysfunctional apoptotic pathway may lead to the development of cancers. Due to the sensitivity of the intrinsic pathway, tumors arise more often through the intrinsic pathway dysfunction than the extrinsic pathway.³⁸

Fas / FasL: Role in Tumor Surveillance

It has been assumed that Fas and FasL works as tumor suppressors, since mutations that down regulate normal function of Fas have been proposed as a mechanism by which tumor cells avoid apoptosis or destruction by the immune system.²⁶

However, a single point mutation of the Fas gene can change Fas/FasL interaction from tumor suppression to tumor promotion by induction of pro-survival genes through non-apoptotic pathways. This dual role of Fas/FasL is found in advanced cancer in humans, resulting in apoptosis resistance and activation of tumorigenic pathways.³⁹

Stimulation of CD95 has been also reported to trigger non-apoptotic pathways.⁴⁰ However, details of CD95-mediated non-apoptotic pathways remain largely unknown. Importantly, it has been shown that membrane-bound CD95L is essential for the cytotoxic activity, whereas soluble CD95L appears to promote autoimmunity and tumorigenesis *via* induction of non-apoptotic pathways, in particular NF- κ B.⁴¹ Future studies are needed to show more details on the mechanism of non-apoptotic action of CD95.⁴²

Fas/FasL: Role in inflammation

Inflammatory biomarkers might help to identify specific inflammatory disturbances. Therefore, targeting specific biomarkers of inflammation might represent new therapeutic approaches.⁴³ Both Fas and FasL proteins exert a wide range of pro-inflammatory functions by inducing secretion of cytokines and chemokines.⁴⁴

Beyond activating apoptosis, the activation of the Fas "DD" can initiate multiple non-apoptotic signaling pathways, including inflammatory responses.^{2,25} Furthermore, Fas/FasL increases cell removal from areas of chronic inflammation,²⁵ through its role in the blockage of apoptosis the soluble form of FasL has been shown to function as a strong chemo-attractant and to enhance neutrophil and phagocyte migration to inflammatory sites.³²

Activation-induced cell death (AICD) down-modulates the immune response.⁴⁵ Therefore, plays a key role in the prevention of inflammatory and auto immune responses. AICD of T-cells, B-cells, and macrophages is mediated by Fas.⁴⁶

Role in eczematous dermatitis

The clinical features of eczema are related to increased blood

flow in the vessels (erythema), augmented vascular permeability (edema), invasion of T-cells into the tissue (infiltration), epidermal spongiosis (vesiculation), and a release of mediators (pruritus). During these eczematous diseases, the resident structural elements in the skin (for example, KCs, 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 dermis and epidermis.⁴⁷

The early acute phase of AE is characterized by a Th2 immune response with a distinct cytokine profile. As the disease progresses, there is a shift to a Th1 response, characterized by CD4+Th lymphocytes and the release of high levels of pro-inflammatory cytokines such as interferon-gamma (IFN- γ), which also helps modulate the transition from acute to chronic inflammation.⁴⁸ The Th1 cytokines released by T-cells in skin, including IFN- γ , can up-regulate Fas expression and increase KC susceptibility to apoptosis.⁴⁹ Additionally, IFN- γ works synergistically with TNF-related apoptosis-inducing ligand (TRAIL) receptor 2 antibody, soluble TRAIL and TNF- α .⁵⁰ In AE, it has been found that T-cells induce the expression of death receptor Fas on the surface of KCs.¹³

FasL, either secreted from activated T-cells or present on their surface, interacts with up-regulated Fas on KCs resulting in apoptosis. KC apoptosis induced by T-cells disrupts the integrity of the skin leading to altered barrier function that favours invasion of allergens, with subsequent production of inflammatory cytokines and amplification of epithelial damage.⁵¹

The eczematous inflammation of the epidermo-dermal unit is caused by the intricate interaction of T-cells and KCs with T-cell-derived inflammatory cytokines, IFNs, and other immune regulatory mediator produced by KCs. Thus the local response of KCs together with the reaction of endothelial cells, T-cells, mast cells, and dendritic cells finally leads to the characteristic clinical and histological symptoms of eczema. It has been suggested that the death Lig and Fas expressed on activated T-cells plays a crucial role in KC death during the elicitation phase of eczematous dermatitis.¹⁴ However, only single KC undergo apoptosis in acute eczema; T-cell-mediated apoptosis of single KCs is a key feature of epidermal pathology in acute eczematous dermatitis.¹⁴ This supports a concept in which the resistance to death Lig and mediated apoptosis may rather define an alternative response of KCs to death receptor ligation.¹³

Damage of KCs decreases the effectiveness of the epidermis as a barrier against invasion by infectious agents. Furthermore, damage to the epidermis might allow greater access of allergens and super-antigens to Langerhans cells, dermal dendritic cells and T-cells, serving to amplify the inflammatory process. Thus, the apoptosis of KCs and damage to the epidermis might play a pivotal role in the development of chronic eczema.¹³

In the skin of patients with eczema, the basal layer of KCs and the basement membrane are morphologically intact. It seems probable that during the course of eczema, KC stem cells located directly at the basal membrane are protected from T-cell induced apoptosis. It has been demonstrated that postmitotic, suprabasal KCs are damaged relatively easily, whereas basal stem cells have strong anti-apoptotic defense mechanisms.⁵²

CD95 is not only needed for a silent end of the life of KCs during eczema but may rather contribute to a “going out with an (inflammatory) bang” intracellular inhibition of effect or caspases or mitochondrial signaling pathways of apoptosis downstream of caspase-8 activation by Bcl-2 family members or inhibitor-of-apoptosis proteins (IAPs).⁵³ might interfere with apoptotic, but not non-apoptotic, signals by death receptors. This scenario may ultimately result in a uncontrolled activation of CD95-mediated inflammation in the skin, but this hypothesis awaits further experimental studies. It will be interesting to determine under which conditions apoptosis may predominate over CD95-mediated inflammation in KCs. This difference subtle at first glance of a death receptor-mediated signal might prove to be highly relevant to the quantitative response in the skin as the target organ of eczematous inflammation.¹³

A common histopathological feature of eczema is the formation of exudative epidermal vesicles that are disruptive to the normal barrier function of the skin. Although vesicle formation in eczema has been largely attributed to rupturing of KCs attachments as a result of inter cellular edema (spongiosis). Recent findings suggest that KC death plays a major role in vesicle formation.⁵⁴ This KCs death appears to be apoptotic and to be mediated by FasL, delivered to the epidermis by infiltrating T-lymphocytes and acting on Fas whose expression on the surface of KCs is induced by T-lymphocyte-derived IFN- γ .¹³

These findings clearly demonstrated the important role of FasL in the epidermal destruction in inflammatory skin diseases. However, whether FasL is directly involved in the inflammatory process is not known. We demonstrate here that FasL elicits a pro-inflammatory reaction in human KCs by triggering the expression of stress-responsive transcription factors, inflammatory cytokines, chemokines, and the adhesion molecule ICAM-1, KC; as a target of Fas-induced apoptosis, provides evidence that this form of cell death contributes to the pathogenesis of eczematous dermatitis. KCs normally express low-levels of Fas, but IFN- γ up-regulates Fas on these cells. Secretion of IFN- γ by T-lymphocytes, which promotes Fas up-regulation in KCs, is a crucial early step in this pathway. Therefore, in this case KC apoptosis occurs only in association with an inflammatory reaction; but it is important to mention that the inflammatory infiltrate is not the consequence but the cause of apoptosis.⁵⁵

From the pathophysiological point of view, it is interesting that the same mechanism is demonstrated in AD and ACD, since these dermatoses are usually regarded as mutually exclusive, AD being a classic example of a Th2-mediated and ACD of a Th1-mediated process.⁵⁶

Some authors speculated that IFN- γ expression *via* up-regulation of the intercellular adhesion molecule 1 (ICAM-1) contributes to the subsequent accumulation of inflammatory cells. Consistent with this suggestion, the present findings imply that the high expression of IFN- γ also propagates the inflammatory process *via* disruption of the epidermal barrier. Interestingly, in histologic sections of AD and ACD lesions alike, the majority of apoptotic KCs were found not in spongiotic regions, but in areas that retained normal cohesion of epidermal cells. Hence, one can speculate that apoptosis precedes spongiosis and, further, that apoptotic death of KCs promotes spongiosis by enabling the in-

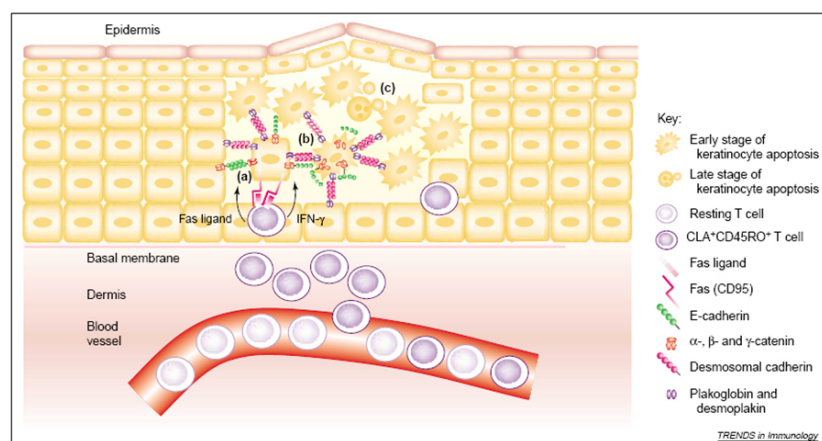


Figure 4: T-cells attack keratinocytes (KCs) in the elicitation phase of eczematous dermatitis. The infiltration of activated CD4⁺ and CD8⁺ T-cells into the dermis and epidermis results in eczematous changes to the epidermis. The apoptosis of KCs is characterized by impairment of the cohesion between KCs (spongiosis). The key pathogenic steps are as follows. (a) Interferon γ (IFN- γ) secreted by activated T-cells (CLA⁺CD45RO⁺) enhances the expression of Fas on KCs. Membrane-bound and soluble FasL and produced by activated T-cells triggers Fas on the KCs. (b) During the early stages of the apoptosis of KCs, E-cadherin is cleaved by caspases that remove the β -catenin-binding domain from its cytoplasmic tail. By contrast, desmosomal cadherins (e.g. desmogleins and desmocollins) remain intact. The intracellular domain of E-cadherin is linked to actin microfilaments through its association with α -catenin, β -catenin and γ -catenin (plakoglobin). Desmosomal cadherins bind to the cytoplasmic proteins plakoglobin and desmoplakin, and are linked to keratin intermediate filaments.¹³ (c) Finally, DNA is fragmented and apoptotic bodies form.

Abbreviation: CLA, cutaneous lymphocyte-associated antigen.

flux of EC fluid into the epidermis (Figure 4).^{13,57-60}

Activated transcription factors, such as nuclear factor kappa B (NF- κ B), activator protein 1 (AP-1), nuclear factor of activated T-cells (NF-AT) and signal transducer and activator of transcription (STAT) factors, induce inflammation and favor the recruitment of CLA⁺T cells to the skin through chemokines and cell-adhesion molecules (e.g. vascular-cell adhesion molecule 1 and E-selection). During the final process of migration, some T-cells penetrate the basal membrane and reach the intercellular space of epidermal KCs. Superfluous and damaged T-cells are removed by apoptosis, promoting the resolution, rather than progression, of inflammation. An increased level of apoptosis controls the number of activated, skin-homing T-cells in peripheral blood, but cytokines (e.g. IL-2, IL-4 and IL-15) and components of the EC matrix (e.g. fibronectin, laminin, tenascin and collagen IV) in eczematous skin prevent T-cell apoptosis. Therefore, the prolonged survival of T-cells, due to components of the skin micro-environment, causes more-pronounced tissue damage and might contribute to chronicity in eczema.^{47,61}

CONCLUSION

It is now clear up that Fas receptor plays an important role in the pathogenesis of some dermatologic diseases. Its role cannot be rolled out as a contributing factor to others. So, better evaluation of such role can help in understanding the pathogenesis of such diseases and also can open a new hope of management of such diseases and the possible use of anti-Fas antibodies in the future.

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