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Editorial

Keratinocytes: Key Immunocytes of the Integument

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Until recently, the integument was primarily viewed by physicians (including dermatologists) as a passive, protective coat.[1] Epidermal keratinocytes comprise over 95% of the cell mass of the outermost portion of skin and were also largely overlooked by immunologists. Keratinocytes, as their name suggests, were primarily studied for their contribution to the structural integrity (via keratin production) and barrier formation (via lipid biosynthesis) of skin.[2] In this review, new developments in the immunobiology of skin will be summarized that highlight the dynamic immunological capabilities of keratinocytes. With respect to the keratinocyte, it is possible to broadly conceive of three distinct immunological roles by which they can interact with T lymphocytes: 1) antigen irrelevant signal transducers; 2) antigen/superantigen specific accessory cells and presenting cells; 3) antigen-specific target cells (Figure 1).

Keratinocytes as Environmental Signal Transducers—Sentinel Function

Two years ago we proposed that keratinocytes could initiate T cell trafficking into the skin by being directly activated in response to a wide variety of environmental cues.[1] Exogenous stimuli mentioned included exposure to ultraviolet light, chemical irritants, and low molecular weight allergens. This outside-in hypothesis completely reversed the prevailing view that the only epidermal consequences for the keratinocyte during cutaneous inflammatory reactions was an inside-out type reaction in which infiltrating dermal leukocytes would cause keratinocyte damage. Thus, keratinocytes were traditionally viewed as nonparticipatory bystanders and innocent victims of secreted toxic products such as oxygen-free radicals, proteases, complement deposition, etc. During the past several years, a compelling body of evidence has been published (see listing of 11 citations in Table 1) that supports our hypothesis regarding the sentinel function of keratinocytes in both murine and human *in vivo* experimental systems.[3–13] The key element of this new proposal involved the rapid and direct ability of keratinocytes to respond to diverse environmental perturbations by producing the cytokines tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β).

Table 1 summarizes the studies detecting or implicating keratinocyte production of TNF-α and/or IL-1β at either the messenger RNA or protein level within minutes or hours of exposing the skin to various stimuli. With respect to the allergens used at challenge sites, it should be emphasized that the keratinocyte response preceded trafficking of T cells into the epidermis.[14,15] This observation also necessitated significant modification of the existing pathophysiological schema for delayed hypersensitivity type of immune reactions in skin. Previous dogma stated that these low molecular weight haptens were required to bind first covalently to a carrier protein and be processed by a Langerhans cell, transported to the local draining lymph nodes, where a sensitized antigen-specific T cell proliferative response would occur, and eventuate within the circulation by the appearance of skin-seeking T cells days later. Whereas this amplification process involving antigen-specific T cells does occur, it

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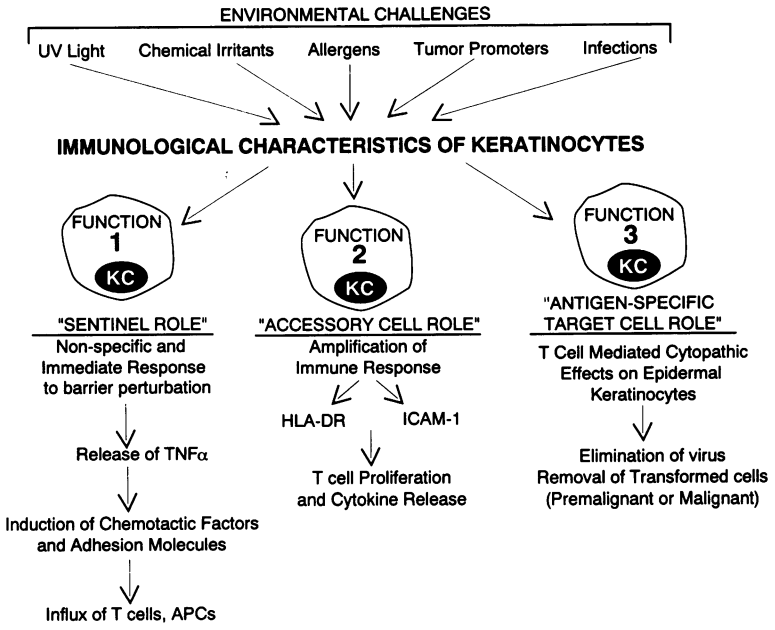

Figure 1. *Cutaneous immune responses to a wide variety of environmental challenges involve the active participation of epidermal keratinocytes. At least three important immunological functions of keratinocytes can be highlighted including: a sentinel role; an accessory cell role; and a target cell role.*

seems to be a distal event relative to the previously unappreciated rapid and direct ability of keratinocytes to become activated (via translocation of protein kinase C from the cytoplasm to the plasma membrane) by allergens such as urushiol (poison ivy antigen) and produce cytokines such as TNF-α/IL-1β. These cytokines could then stimulate the neighboring endothelial cells to express adhesion molecules such as endothelial leukocyte adhesion molecule-1, vascular cell adhesion molecule-1, and intercellular adhesion molecule-1 (ICAM-1). Such a paracrine type of endothelial cell activation by the keratinocytes would facilitate the subsequent influx of memory T cells from the blood stream. Perhaps the most definitive evidence that epidermal keratinocytes can influence the vasculature comes from gene transfer experiments. Using apolipoprotein-producing keratinocytes, it has been demonstrated upon placement of such genetically altered keratinocytes in the epidermal compartment that circulatory blood levels of apolipoprotein A can be detected.[16]

It is also worth noting that clinicians previously viewed irritant and allergic contact dermatitis reactions as being derived from two very distinctive pathways, but the recognition that activated keratinocytes participate in the early phases of both reactions provide a common cellular link. Such a molecular connection helps explain the clinical overlap that can occur in the earliest phases of irritant and allergic contact reactions of the skin that makes them indistinguishable at times.

Returning to the earliest detectable transcriptional events in the epidermis following the aforementioned stimuli, we must ask what is the unifying feature that could explain this final common molec-

Table 1. *Keratinocytes in Vivo Directly and Rapidly Produce TNF-α and/or IL-1β*

Stimulus	Source of Skin	Investigators[2]
Repeated tape stripping	Mouse	Elias et al[3]
	Human	Nickoloff and Naidu[4]
Ultraviolet irradiation	Human	Ansel et al[5]
		Oxholm et al[6]
		Norris et al[7]
	Mouse	Kurimoto and Streilein[8]
Irritant (sodium lauryl sulfate)	Human	Gatto et al[9]
		Hunziker et al[10]
	Mouse	Enk and Katz[11]
Allergen: poison ivy antigen (urushiol)	Human	Griffiths et al[12]
dinitrochlorobenzene		
	Mouse	Piquet et al[13]
	Mouse	Enk and Katz[11]

ular pathway. A definitive answer is not currently available, but we believe a plausible explanation can be put forward that involves the outermost epidermal keratinocytes. These upper level cells are critically important in producing the stratum corneum, which is responsible for the barrier function of skin.[17] By immunostaining, TNF-α is localized to these outermost keratinocytes.[18] Because both irritant and allergic contact reactions can perturb the barrier function of skin (as determined by increase in transepidermal water loss), it is likely that preformed TNF-α is released and made available to keratinocytes during barrier abrogation. The adjacent keratinocytes possess unoccupied high-affinity receptors for TNF-α[19] and thus could initiate the cytokine cascade. From *in vitro* studies, we know that TNF-α can auto-induce itself,[20] and hence one can visualize how these upper level keratinocytes could self-stimulate additional TNF-α production during the avalanche of molecular events that begin from the outside of the skin and proceeded inward.

Before leaving this topic, it is also important to consider how neighboring cells can interact with keratinocytes during this response to injury. The other relevant endogenous cell types to be considered include resident Langerhans cells, intraepidermal free nerve endings, and mast cells.[21–23] These other cell types may play a role in various acute dermatitis reactions because certain plants have the capacity to induce reactions in the skin mediated via histamine and substance P even without perturbation of the barrier.[24] Langerhans cells may be important in the earliest phases of cutaneous reactions because they can produce interferon-γ (IFN-γ) after exposure to contact sensitizers.[25] Based on polymerase chain reaction results, IFN-γ messenger RNA can be detected in normal, uninflamed skin, and as keratinocytes do not produce IFN-γ, the Langerhans cell is an obvious candidate for the cell of origin for this positive polymerase chain reaction signal.[26] Of course, even normal skin contains rare intraepidermal T lymphocytes, and we cannot entirely dismiss their potential contribution to IFN-γ production.[11] Nonetheless, the early appearance of IFN-γ could provide strong synergistic enhancement for keratinocyte ICAM-1-mediated by TNF-α.[27] With respect to IFN-γ and TNF-α, we have recently explored how other molecules produced in or near the epidermis could modulate their ability to induce keratinocyte HLA-DR and ICAM-1 expression. Table 2 summarizes the results available for cultured keratinocytes using cis-urocanic acid (cis-UCA), all-trans UCA, histidine, histamine, and substance P.

Table 2. *Influence of Endogenous Mediators on TNF-α and IFN-γ Induction of Keratinocyte ICAM-1 and HLA-DR Expression**

	ICAM-1	HLA-DR
Untreated	4	3
IFN-γ (10 U/ml)	58	45
TNF-α (50 U/ml)	9	3
TNF-α (500 U/ml)	26	3
Histamine (5 mmol/L)	8	3
Histidine (5 mmol/L)	4	3
Cis-UCA (2.4 mmol/L)	7	3
All-trans UCA (5 mmol/L)	4	3
TNF-α (50 U/ml) plus histamine (5 mmol/L)	38	3
TNF-α (50 U/ml) plus cis-UCA (2.4 mmol/L)	35	3
IFN-γ (10 U/ml) plus cis-UCA (2.4 mmol/L)	26	28
IL-1β (50 U/ml)	12	3
IL-1β (50 U/ml) plus histamine (5 mmol/L)	34	3
IL-1β (50 U/ml) plus cis-UCA (2.4 mmol/L)	22	3
Substance P (SP) (0.5 mmol/L)	14	3
SP (0.5 mM) plus IFN-γ (10 U/ml)	232	48
SP (0.5 mM) plus TNF-α (500 U/ml)	43	4

* Representative mean channel fluorescence values as determined by fluorescence-activated cell sorter analysis of multipassaged human keratinocytes before and 48 hours after indicated treatment; isotype control values are less than 3. The first 11 lines of results are from previous publications.[29,31] The remaining data represent unpublished results (RS Mitra and BJ Nickoloff).

Cis-UCA was selected because it is rapidly produced from trans-UCA upon exposure to ultraviolet light and has immunomodulatory properties.[28] The differential ability of ultraviolet light to enhance allergic contact dermatitis reaction when used during the challenge (or ellicitation) phase may be due to the ability of cis-UCA to enhance TNF-α-mediated induction of keratinocyte ICAM-1.[29] Conversely, ultraviolet light exposure before initial sensitization suppresses subsequent challenge phases,[21,30] and this phenomenon may relate to the ability of cis-UCA to suppress IFN-γ-mediated induction of keratinocyte HLA-DR expression.[31] As can be seen, all-trans UCA and histidine had no effect on the interaction of TNF-α with keratinocytes. Interestingly, both histamine and substance P (which can induce histamine release from mast cells) were capable of influencing keratinocytes directly, either alone or in combination with TNF-α/IFN-γ. Thus, there is a wide variety of endogenously derived soluble noncytokine factors that can influence cytokines produced

by resident epidermal and dermal cell constituents thereby contributing to the sentinel function of keratinocytes.[32]

Keratinocytes Can Function as Accessory Cells and Antigen-Presenting Cells

In contrast to the previous section, which primarily emphasized cytokines, this section will focus on molecules located on the surface of keratinocytes that facilitate interactions with T cells. That the keratinocyte may be an immunocyte (ie, antigen-presenting cell) was initially raised by the discovery that IFN-γ could induce major histocompatibility complex class II antigens HLA-DR and HLA-DQ on cultured keratinocytes. *In vivo*, a large number of T cell-mediated skin diseases are characterized by aberrant expression of HLA-DR.[33] Additionally, it was also demonstrated that IFN-γ treatment of keratinocytes could promote adhesion of T cells by inducing ICAM-1 on keratinocytes, thereby facilitating binding by leukocyte function antigen-1-bearing T cells.[34,35] When keratinocytes express HLA-DR and ICAM-1, this phenotypic change is accompanied by important new functional capabilities. As recently demonstrated, IFN-γ-pretreated keratinocytes are very effective accessory cells when resting autologous T cells are stimulated by either of the following: mitogenic lectin-phytohemagglutinin, bacterial-derived superantigens, and immobilized CD3 monoclonal antibody.[36] With respect to the bacterial-derived superantigen-mediated stimulation, this accessory cell function of keratinocytes was strongly dependent on lymphocyte function associated antigen-1/ICAM-1 interaction. Another group of investigators, using phorbol ester-activated keratinocytes to induce ICAM-1, has also observed a co-stimulating role of keratinocytes for T cell activation.[37] The pathophysiological implications of these developments, particularly related to T cell-mediated skin diseases triggered by bacterial infection such as psoriasis and atopic dermatitis are discussed elsewhere.[36] Besides ICAM-1 and HLA-DR, keratinocytes can also express a CD28 ligand recognized by the antibody BB-1 that is distinct from the B7 ligand expressed on B cells and monocytes.[38] In several other types of immune reactions, CD28 on T cells is an important co-stimulatory molecule,[39] and it remains to be determined what are the immunological consequences of keratinocyte BB-1 expression in diseases such as psoriasis. Despite the current lack of functional correlation, it was studying the immunological properties of keratinocytes that led to the discovery that BB-1 and B7 are not identical antigenic entities.

When IFN-γ-treated keratinocytes are examined for their ability to present either allo-antigen or nominal antigens, they seem to possess yet another type of immunological function. For nominal antigens, rather than serving to stimulate T cells as we observed for superantigens, the net immune response is a tolerogenic signal that is antigen specific.[40,41] Apparently, even though these same types of activated keratinocytes can provide accessory signals for several other stimuli (ie, lectin, superantigens, immobilized CD3),[36] when nominal or allo-antigens are involved, the BB-1/ICAM-1/HLA-DR-positive keratinocytes cannot generate a positive T cell response.[42–44] The nature of this antigen presentation defect is unknown but under active investigation because elucidating this pathway may have tremendous implications for clinicians who desire to tolerogenize purposefully an individual to a specific antigen, eg, for occupational dermatitis due to contact allergens in the workplace. As alluded to above, it is possible that BB-1 is a nonstimulating ligand for CD28[36] and hence may be one of the molecular mediators of tolerance. Finally, with respect to the antigen-presenting capacity of keratinocytes, it should be noted that using *Mycobacterium leprae* antigens, including heat shock proteins, keratinocytes could stimulate CD4+ T cell proliferation.[45] Thus, there is still a considerable number of somewhat perplexing phenomena related to the antigen-presenting capability of keratinocytes remaining to be understood.

Keratinocytes as Targets of Skin-Specific T Cells

Preferential homing of distinct T cell subsets into the skin has been observed for several decades, but the molecular basis for this phenomenon has only recently been defined. HECA-452 on T cells and endothelial leukocyte adhesion molecule-1 on endothelial cells have been suggested to subserve this skin seeking behavior.[46,47] When a T cell goes through all of the complicated and sequential steps from the initial interaction with vascular endothelial cells to ultimately entering the epidermal compartment, several potentially important types of reactions can occur. First of all, upon binding between a T cell and keratinocyte, the keratinocyte can be activated to produce cytokines such as TNF-α.[48] Such a keratinocyte activation event could lead to autostimulation and expansion of the size of a psoriasis

lesion from a small, pin-point macule to a large plaque. Secondly, the keratinocyte can be targeted for destruction. In terms of human papilloma viral-mediated skin diseases, two articles have recently appeared in the American Journal of Pathology that address this issue.[49,50] If a transformation event occurs in the keratinocyte via an oncogenic subtype of human papilloma virus, then cultured keratinocytes begin to constitutively express ICAM-1. In this issue of the journal, Coleman et al correlate the extent of keratinocyte ICAM-1 expression *in vivo* for cervical neoplasia, noting that high-grade lesions have more abundant ICAM-1 expression and consequently increased intraepithelial trafficking of T cells presumably capable of destroying neo-antigens on the tumor cell surface.[50] The oncological implications for their observations are obvious and may also extend to the cytotoxic T cell response to herpes simplex viral infections of the skin[51] either directly or indirectly as has been suggested for herpes-associated erythema multiforme lesions.[52] Earlier this year, another group interested in the immunology of papilloma viral infection and keratinocytes observed that T cells became activated when they enter the epidermal compartment of a regressing papilloma.[49] These investigators suggest that such T cell activation may play a role in suppression of tumor cell proliferation. Thus, it is becoming clear that virally infected keratinocytes can influence the immune function of T cells in several clinical settings ranging from common and nuisance cutaneous warts, to recurrent T cell dermatoses, to more serious premalignant and invasive epithelial cell-derived malignancies.

Just as a chameleon can change its skin color depending on its local environment to protect itself from predators, the keratinocyte can change its phenotype depending on its environmental perturbation to maintain cutaneous immunohomeostasis. In normal, uninflamed skin in the absence of environmental cues, keratinocytes primarily function to produce an epidermal barrier by synthesizing keratins and lipids. But they also create a cytokine sink in the stratum corneum for a rapid response when the skin is damaged.[53] When the epidermal barrier is broken, this abrogation initiates a proposed cytokine cascade[4] that prepares the keratinocyte for the task of dealing with foreign microbial antigens/superantigens, neo-antigens, or tumor cell antigens. Possible consequences of this response to injury such as keratinocyte–T cell interactions include one or more of the following: further keratinocyte activation, polyclonal T cell activation, antigen-specific T cell proliferation, antigen-specific T cell anergy, or cytotoxicity of the keratinocytes. In any of these scenarios, it is no longer appropriate to ignore the relevance or importance of the keratinocyte. Rather, it is abundantly clear that keratinocytes should be recognized as full-fledged immunocytes that actively and importantly contribute to the initiation, perpetuation, and termination of immune processes that affect the skin.

In conclusion, as residing in the outer portions of the body, keratinocytes can serve as a sentinel cell detecting and responding to environment changes. The sentry response includes an impressive armamentarium of cytokines, chemotactic polypeptides, and adhesion molecules facilitating interaction with T cells. This new appreciation of the immunological function of keratinocytes requires a significant revision of several pathophysiological pathways, and opens new windows of opportunity for novel therapeutic approaches targeted at inflammatory, immunological, and neoplastic disease processes that occur in skin. Finally, it should be emphasized that epithelial cells in other extracutaneous organs (such as thymic epithelium/Hassall's corpuscles)[3] may also be serving important immunological functions, such as those described for keratinocytes in the skin.

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