The Role of Keratinocyte Cytokines in Inflammation and Immunity

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Over the past decade there has been an exponential increase in the number of publications reporting the presence of various immunoregulatory molecules in the epidermis, as illustrated by preceding papers in this supplement. The unequivocal identification of the factors or cytokines owes much to developments in molecular biologic techniques in the last decade. The availability of nucleic acid probes for these molecules and the introduction of sensitive molecular techniques such as northern blotting, in situ hybridization, and the polymerase chain reaction have made the localization of a given cytokine to a particular cell type much more definitive.

IMMUNOLOGIC FUNCTIONS OF THE KERATINOCYTE

In the late 1970s studies of the disease cutaneous T-cell lymphoma, which is characterized by epidermal infiltration by malignant T cells, led Edelson to propose that in normal skin there could be an interaction between the epidermis and circulating T cells [1]. This concept gained further support from the observations that keratinocytes produced a thymopoietin-like molecule [2] and that lymphocytes could be induced to differentiate by factors produced by epidermal cell cultures [3].

Streilein, in 1978, was the first to postulate the existence of a skin-associated lymphoid tissue (SALT) (reviewed in [4]). It is now clear that the skin immune system consists of several other cell types, including Langerhans cells, veiled cells, tissue macrophages, neutrophils, mast cells, vascular endothelial cells, "homing" T cells, and keratinocytes [5].

The discovery that epidermal cells produce an IL-1-like factor which promotes the proliferation of mitogen-stimulated thymocytes [6,7] confirmed the ability of the keratinocyte (KC) to initiate immune responses. These discoveries resulted in greater interest in the role of the KC in immune modulation and have led to the observation that many other cytokines are produced by the KC (see Table I).

The cytokines listed in the Table I are those for which a function in the skin is best understood. Most of these molecules are involved in the initiation of inflammation, leukocytosis, and the acute phase response. Several investigators have looked for but failed to find IL-2, IL-4, IL-5, or interferon gamma (IFN-γ) in KC [13,17]. Let us examine some possible functions of the KC cytokines during a physical injury to the skin with accompanying microbial invasion. Figure 1 illustrates the variety of cells and tissues that can be influenced by KC cytokines. Because IL-1 is produced constitutively by KC and retained in the cell, the epidermis is a vast reservoir of sequestered IL-1 [18]. Damage to the KC releases this IL-1, which essentially is a primary event in skin defense. IL-1 stimulates further release of IL-1 from neighboring KC, thus amplifying the response.* IL-1 also stimulates the production and release of IL-8 [12,19], IL-6 [11], and GM-CSF [20] from neighboring KC. These cytokines are activators for pro-inflammatory cells. IL-8 recruits neutrophils, macrophages, and T cells to the injury site [19,21]. Macrophages and epidermal Langerhan cells present foreign antigens to T cells which then rapidly proliferate under the effect of IL-1. These activated T cells also begin to produce IL-2, IL-4, and IL-5, which stimulate B-cell proliferation and antibody production [22,23]. TNFα release from IL-1-stimulated KC and macrophages enhances the inflammatory responses initiated by IL-1 [24]; it also enhances MHC expression and antigen presentation to lymphocytes [25].

In addition to being directly chemotactic for leukocytes, IL-1 and TNFα induce the expression of intercellular adhesion molecules (ICAMS) on the surface of endothelial cells and fibroblasts [26–28]. These are recognized by circulating leukocytes which adhere to the ICAM-expressing cells at the site of injury. These leukocytes may then become activated by local inflammatory cytokine concentrations. Interferon gamma release by activated T cells stimulates ICAM and MHC class II HLA-DR antigen expression on KC [29,30] facilitating lymphocyte adhesion and antigen presentation. Thus, by cytokine cascades and networks, an inflammatory response can be rapidly generated.

GM-CSF inhibits the migration of mature granulocytes at the site of injury. It also prolongs the survival of these phagocytic cells by inducing superoxide anion production and enhancing antibody-dependent cellular cytotoxicity. GM-CSF increases the antimicrobial capacity of these cells [18] and the antigen-presenting capability of Langerhan cells [31]. G-CSF enhances neutrophil phagocytosis, and M-CSF potentiates the cytotoxicity of mature macrophages [32]. IL-3 is a growth factor for mast cells [33] and may be involved in allergic reactions. Parasitic infections appear to be limited by the degranulation of mast cells; therefore, IL-3 release may be indirectly involved in antiparasitic mechanisms. The hematopoietic colony-stimulating factors released by the skin may also stimulate the bone

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Abbreviations:
CSF: colony-stimulating factor
G-CSF: granulocyte colony-stimulating factor
GM-CSF: granulocyte-macrophage colony-stimulating factor
HSF III: hepatocyte-stimulating factor III
ICAM: intercellular adhesion molecule
IFN-γ: interferon gamma
IL: interleukin
KC: keratinocyte
M-CSF: macrophage colony-stimulating factor
MHC: major histocompatibility complex
SALT: skin associate lymphoid tissue
TNFα: tumour necrosis factor alpha

* Sauder DN (unpublished observations).

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Table I. Pro-Inflammatory Cytokines Produced by Keratinocytes

Cytokine	Reference
IL-1α	[8]
IL-1β	[9]
IL-3	[10]
IL-6	[11]
IL-8	[12]
Granulocyte colony-stimulating factor (G-CSF)	[13]
Macrophage colony-stimulating factor (M-CSF)	[13]
Granulocyte-macrophage colony-stimulating factor (GM-CSF)	[14]
Tumour necrosis factor alpha (TNFα)	[15]
Hepatocyte stimulating factor III	[16]

marrow to replenish the complement of myeloid cells lost through blood loss or in fighting infection, but this is not clear at present. IL-1 synergizes with the CSF, stimulating hematopoiesis [34]. KC and IL-1-activated monocytes also release IL-6 [11]. Interleukin-6 promotes both B-cell growth and differentiation and stimulates T-cell proliferation and natural killer cell activation [35]. The most important function of IL-6 is probably the induction of acute phase protein synthesis in the liver. This diverse collection of proteins includes proteinase inhibitors and other proteins whose purpose is to terminate the inflammatory response and restore normal homeostasis [35]. Interleukin-1, TNFα, and hepatocyte stimulatory factor III are also inducers of acute phase proteins [16,36], although the spectrum of proteins that they induce differs from that induced by IL-6 [37].

IL-1 stimulates KC chemotaxis, proliferation, and fibroblast proliferation, [38–40] and when applied topically, increases the rate of healing of split thickness wounds [41]. Similarly, IL-6 has been shown to be an autocrine growth factor for KC [42] and thus may also be involved in wound healing. Interestingly, in psoriasis, a disease of epidermal hyperplasia, levels of both of these cytokines have been demonstrated to be elevated in lesional tissue [43,44].

The fact that the skin is the body's first line of defense against microbial invasion is reason enough for having a rapid response system of immune regulation located there. This allows a rapid mobilization of the cellular arm of the immune system to the sites where the skin has been breached. The systemic effects of these cytokines also ensures co-ordination and control of the whole body's defense and homeostatic mechanisms.

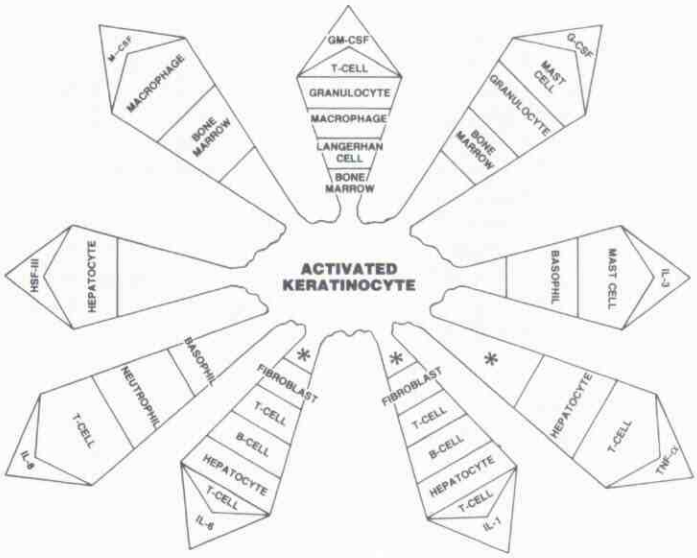

Figure 1. Cytokines produced by activated or damaged keratinocytes and their cellular targets.*, multiple cellular targets.

Most of the interest in KC cytokines over the last decade has focused on pro-inflammatory or immunologically stimulatory cytokines. There tends to be an unbalanced leaning of interest toward this type of regulator, although it is just as important for the immune response to be down-regulated when no longer appropriate. Negative regulators may be equally important in homeostatic terms for shutting down the immune response once infection or immunologic insult has been suitably resolved. Malfunction in the mechanisms controlling these responses may be the key to autoimmune diseases and allergy.

PRO-INFLAMMATORY CYTOKINES AND EPIDERMAL DISEASE

Many molecular models of disease propose that a breakdown in the regulation of growth factor production and signal transduction results in abnormal proliferation and cell behavior. Currently, abnormal cytokine production is being studied as a mechanism in dermatoses. Several points suggest that this may be a fruitful course to pursue. i) Abnormally high levels of inflammatory cytokines are found in several different inflammatory skin conditions; for example, IL-1 in cutaneous T-cell lymphoma [45] and IL-8 and IL-6 in psoriasis [43,46]. ii) The above cytokines recruit pro-inflammatory cells to the epidermis by exerting direct chemotactic stimuli or by induction of adhesion molecules. Indeed, up-regulation of ICAM expression on KC is a consistent feature of atopic dermatitis, psoriasis, mycosis fungoides, and lichen planus, although non-lesional skin showed no ICAM staining [47,48]. iii) Elevated concentrations of growth factor may transform or activate infiltrating T cells in a paracrine fashion and maintain them in an activated state [49,50].

Such paradigms have many mechanistic merits and can be readily tested for validity. However, the question remains whether cytokine abnormalities represent the egg or the chicken in dermatologic disorders.

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