

Review article

The role of cytokines and neuroendocrine hormones in cutaneous immunity and inflammation

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Cytokines are low-mol.-mass (glyco) proteins which are produced transiently by almost any eukaryotic cell, and which act via specific cell-surface receptors. Cytokines have multiple overlapping activities (10); they may induce each other or influence the expression of their receptors, and thus they can affect cell function in a synergistic, additive, or antagonistic way. This suggests the existence of a network of interacting cytokines called the cytokine cascade. The cytokine family consists of interleukins (IL), chemokines (CK), tumor-necrosis factors (TNF), colony-stimulating factors (CSF), interferons (IFN), growth factors, and suppressor factors. This review will mainly focus on cytokines of special significance for the regulation of cutaneous immune and inflammatory responses, and most other mediators will be mentioned only briefly.

Nonspecific proinflammatory cytokines

Interleukin-1 (IL-1)

Two different subtypes of IL-1 named α and β have been described which share the same broad spectrum of biologic activities and bind to common re-

ceptors (22, 28). Moreover, a physiologic antagonist belonging to the IL-1 gene family has been identified. Because its structure is like that of IL-1, it competes with the binding of the natural ligand to the receptor, but does not have IL-1 activity; thus, it is called the IL-1 receptor antagonist (IL-1RA) (24).

The biologic activities of IL-1 include thymocyte costimulation, induction of cytokine and growth factor release, IL-2 receptor expression and chemotaxis of T cells, enhancement of the effects of B-cell stimulatory factors, and augmentation of cytotoxic activity by macrophages. The effects of IL-1 on hematopoietic stem cells include costimulation of colony-stimulating factor (CSF) activities (22). Moreover, IL-1 is an important inflammatory mediator; it induces fever, as well as production of acute-phase proteins, and causes an inflammatory infiltrate when injected into the skin (23). Endothelial cells stimulated by IL-1 produce cytokines and express surface molecules such as intercellular adhesion molecule (ICAM-1), as well as the endothelial cell leukocyte adhesion molecule (ELAM-1), which are important in endothelial cell leukocyte interactions in vasculitis (22). Recently, IL-1 was also found to participate in neuroendocrine immune in-

teractions by stimulating the release of hypothalamic and pituitary gland hormones such as proopiomelanocortin (POMC)-derived peptides (93).

IL-1 α has been shown to be a cofactor supporting Langerhans' cell viability in culture, and membrane-bound IL-1 α serves as a costimulatory factor for Langerhans' cell antigen presentation to Th2, but not Th1, lymphocytes (90). Moreover, IL-1 appears to be a significant chemoattractant for Langerhans' cells, because injection of IL-1 into the cornea, which usually does not harbor Langerhans' cells, results in a significant influx of Langerhans' cells into the corneal epithelium (75). Recently, it was shown that injection of IL-1 β into murine skin induces the same morphologic and functional alterations of Langerhans' cells as topical application of contact allergens, i.e., retraction of Langerhans' cell dendrites, emigration of Langerhans' cells out of the epidermis into the draining lymph nodes, and rapid and dramatic upregulation of MHC class II molecules on the surface of epidermal Langerhans' cells (29). These activities appear to be specific for IL-1 β , because IL-1 α did not exert these effects when administered in comparable doses, but led to a down-regulation of Langerhans' cell antigen-presenting function (29, 37). These data indicate that IL-1 α and IL-1 β may have differential effects for the regulation of cutaneous immune responses such as contact hypersensitivity (CHS). Because IL-1 α and IL-1 β bind to both types of IL-1 receptors, these observations suggest functional differences in signal transduction via the type I or type II IL-1 receptor. The *in vivo* relevance of these findings is supported by the fact that injection of anti-IL-1 β antibodies completely blocks the sensitization phase of CHS (29). Moreover, in patients with allergic rhinitis, the clinical course of cutaneous allergic late-phase response after intradermal injection of a relevant allergen was inhibited by immediate subcutaneous application of soluble IL-1R (73).

Interleukin-6 (IL-6)

IL-6 is a pleiotropic cytokine released by almost any cell upon appropriate stimulation. There is evidence of a high frequency of restriction fragment polymorphism in the IL-6 gene, but it is not yet known whether this has any biologic implications (103). High-affinity IL-6 receptors are expressed on various cells and cell lines including keratinocytes (107, 117). Several cytokines such as leukemia-inhibitory factor (LIF), oncostatin M, ciliary neurotrophic factor, and interleukin-11 share a common signal-transducing receptor (gp130) and thus have IL-6-like activities (76, 118).

IL-6 is an important inflammatory mediator; it activates the production of acute-phase proteins, in-

hibits the secretion of albumin, and induces fever. The involvement of IL-6 during systemic inflammation is supported by the finding of elevated IL-6 serum levels in patients with inflammatory or autoimmune diseases. IL-6 mediates in the final differentiation of B cells into immunoglobulin-secreting plasma cells and induces the proliferation of certain transformed B-cell lines (3, 103). The role of IL-6 in tumor development is controversial because IL-6 may stimulate or inhibit differentiation and proliferation, depending on the tumor type (103). IL-6 can also function as an accessory signal required for thymocyte and T-cell proliferation. Moreover, it is a differentiation factor for cytotoxic T cells and stimulates the activity of natural killer (NK) cells (58, 100). IL-6 synergizes with colony-stimulating factors, in the stimulation of the proliferation and differentiation of hematopoietic stem cells (44). The crucial *in vivo* role of IL-6 in immunity and inflammation is shown by the impaired immune and acute-phase responses in IL-6-deficient mice (53).

In addition to keratinocytes, cultured, but not freshly isolated, epidermal Langerhans' cells have been shown to express large amounts of IL-6 mRNA and protein (51, 96). The significance of the upregulation of IL-6 production in cultured Langerhans' cells for antigen presentation is still unclear. However, it was recently shown that IL-6 *in vivo* may suppress both the induction and the effector phase of delayed-type hypersensitivity (DTH) (67).

Tumor necrosis factor- α (TNF- α)

TNF- α was originally described as a macrophage-derived cytokine which mediates tumor necrosis and cachexia; thus, it was called "cachectin". Another cytotoxic factor released by lymphocytes was initially named "lymphotoxin" and is now called "TNF- β ". Although TNF- α and TNF- β are antigenically distinct proteins, they exhibit similar biologic activities and bind to common receptors (1). Two different types of TNF receptors (TNFR) bind TNF- α and TNF- β with high affinity, but are differentially expressed on many cells. As shown for other receptors, soluble TNFR, still retaining their binding capacity, have been found in body fluids and cell-culture supernatants (1). TNF receptors belong to a receptor-gene superfamily of cellular and viral proteins termed "the TNF-receptor superfamily", which comprises at least 12 members. Among the pleiotropic biologic effects of ligands, they share the unique ability to induce apoptosis (104).

TNF- α is secreted by various cells and has a broad spectrum of biologic activities. It induces fever and activates inflammatory cells, including neutrophils, eosinophils, and macrophages. Endothelial cells respond to TNF- α with proliferation, production of

cytokines, and expression of adhesion molecules such as ICAM-1. Moreover, TNF- α induces MHC class I and II antigen expression on various cells and costimulates T and B cells, as well as hematopoietic stem cells (1, 23). Keratinocytes which were found to express only TNFRII respond to TNF- α with increased expression of ICAM-1, possibly being of importance in T-cell-keratinocyte interactions (110).

Recently, it has been shown that incubation of peripheral blood mononuclear cells (PBMC) in the presence of granulocyte/macrophage CSF (GM-CSF) and IL-4 resulted in the outgrowth of a cell line with an antigen-presenting capacity like that of immature dendritic cells (DC). Treatment of this DC line with TNF- α resulted in an increased T-cell stimulatory capacity in the mixed lymphocyte reaction (MLR), but in a decreased presentation of soluble antigen (92). TNF- α also has been found to be critically involved in the elicitation phase of CHS and DTH responses. Accordingly, injection of TNF- α into the skin induces CHS-like effects, and the elicitation of CHS could be blocked effectively by injection of TNF- α antibodies (80, 106). Moreover, the release of TNF- α by epidermal cells upon UV exposure causes UV-induced suppression of the ability to induce CHS responses in UVB-irradiated skin (106). The important role of TNF- α in the effector phase of CHS is further supported by the recent observation that the xanthine derivative pentoxifylline, which blocks the production of TNF- α , can suppress CHS reactions in man and mice (99, 101).

There appear to be genetically determined differences in susceptibility to the immunosuppressive effects of UVB in both mice and man. The UVB sensitivity of mice with regard to the suppression of the induction phase of the CHS response may be linked to a polymorphism within the TNF- α gene locus (106). Consequently, it has been postulated that TNF- α exerts its suppressive effect during the sensitization phase of CHS by immobilizing epidermal Langerhans' cells within the epidermis for a significant period of time (105). Accordingly, antigen-bearing, epidermal Langerhans' cells cannot migrate into the draining lymph nodes, where they interact with naive T cells, leading to sensitization. Moreover, the enhancement of the elicitation phase of CHS by UVB may also be explained either by the direct proinflammatory and vasodilatory effect of TNF- α , or by an immobilization of epidermal Langerhans' cells within the epidermis, where they ultimately lead to increased antigen presentation to primed T cells during the elicitation phase of CHS (81).

Chemokines (CK)

The term "chemokines" (CK) comprises a supergene family of proinflammatory and chemotactic cytokines characterized by the presence of four conserved cysteines (97). One subfamily contains members characterized by the presence of a single amino acid between cysteines 1 and 2 (C-X-C family). These mediators are chemotactic preferentially for neutrophils and include IL-8 and melanoma-growth-stimulating activity/growth-related gene product (MGSA/GRO). The second group in which the amino acid between the cysteines is lost (C-C family) comprises mediators which are not chemotactic for neutrophils, but which attract other leukocytes. Members include monocyte chemotactic activating factor/monocyte chemotactic protein 1 (MCAF/MCP-1), MCP-3, RANTES (regulated on activation, normal T expressed, and secreted), murine macrophage inflammatory protein 1 α (MIP 1 α), and MIP-1 β and their human equivalents LD 78 and PAT 744 (9, 65, 97).

Many different cells, including keratinocytes, can serve as a source for IL-8, which stimulates chemotaxis and enzyme release of neutrophils, and which is chemotactic for basophils, lymphocytes, and keratinocytes (97). Increased amounts of IL-8 were found in "neutrophilic dermatoses" such as psoriasis and palmoplantar pustulosis. High-affinity receptors for IL-8 proteins are expressed on neutrophils and on myelocytic cell lines (97).

MCP-1, which belongs to the C-C-family, is released by monocytes, fibroblasts, endothelial cells, and keratinocytes. The last-named were found spontaneously to express MCP-1 mRNA and to secrete the protein after stimulation by IFN- γ (11, 36). MCP-1 is chemotactic for monocytes, as well as basophils, and stimulates histamine release by basophils and mast cells (54). Moreover, C-C chemokines have been found to be activated and to be chemotactic for eosinophils. MCP-3 stimulates histamine release by basophils and, as RANTES, is chemotactic for both eosinophils and basophils (97). Recently, it has been shown that MIP-1 α , another member of the C-C-family, is produced by murine Langerhans' cells (9, 64). This appears to be of special interest because MIP-1 α inhibits the proliferation of keratinocytes and stem-cell differentiation. Moreover, MIP-1 α is chemotactic for memory T cells, whereas MIP-1 β functions as a chemoattractant for naive T cells (97).

In addition to lymphocytes and antigen-presenting cells, mast cells, basophils, and eosinophils are critically involved in hypersensitivity reactions. Because of their activating and chemotactic capacities, C-C chemokines can be regarded as crucial signals for the accumulation of these effector cells in inflamma-

tory and particularly allergic diseases. Moreover, cytokines released by Th2 cells, such as IL-3, IL-4, IL-5, and GM-CSF, have been shown to be of importance in priming basophils and eosinophils for the release of their mediators. This priming phenomenon, resulting in an amplification of the effects of chemokines, may play an important role in allergic diseases and explain the increased sensitivity observed in patients upon repeated allergen exposure or in the case of an infection associated with increased cytokine production (9).

Cytokines affecting lymphocyte functions

Interleukin-2 (IL-2)

The discovery of IL-2, which was originally described as T-cell growth factor (TCGF), had a major impact in immunology because it enables the growth of T cells in culture and consequently the study of their functions (91). IL-2 is produced by T cells in response to activation by antigens or mitogens. It initiates the proliferation of T cells via binding to specific, high-affinity IL-2 receptors which are not expressed on resting T cells, but which rapidly appear after stimulation. Upon elimination of the stimulus, the transcription of IL-2 and IL-2 receptor genes is downregulated, followed by cessation of T-cell proliferation (115). IL-2 augments T-cell cytotoxicity, enhances the activity of NK cells, and induces the expansion of tumor-specific cytotoxic cells. Furthermore, activated B cells expressing the IL-2-receptor β -chain can be driven into differentiation by IL-2 (108). There is also evidence that keratinocytes express IL-2 receptors although the potential effects of IL-2 on keratinocytes are not yet clear (25).

Interleukin-4 (IL-4)

B-cell-stimulating factor 1, which later was renamed interleukin-4 (IL-4), turned out to have a broad spectrum of effects not only on B but also on T cells. The major source of IL-4 is Th2 cells, a subset of CD4⁺ lymphocytes (78). There is also recent evidence that keratinocytes under certain circumstances may express IL-4, showing for the first time production of IL-4 by nonhematopoietic cells (6). IL-4 exerts its biologic effects via high-affinity receptors which are present on T and B cells, mast cells, macrophages, stem cells, fibroblasts, epithelial cells, and Langerhans' cells (16, 78, 90). In addition to being a B-cell growth factor, IL-4 induces the expression of class II MHC molecules, as well as of the low-affinity receptor for IgE, and acts as a potent stimulant of IgG1 and IgE secretion by B cells. It also has been found to upregulate the expression of MHC class II molecules as well as all three types of Fc ϵ -receptors on human Langerhans' cells (14, 15).

Furthermore, IL-4 upregulates IL-4 receptors and is a growth factor for some T cells and mast cells. It also activates macrophages and acts on multiple hematopoietic cell lineages (46, 78). Several effects of IL-4 on B cells and macrophages, but not on T cells, can be inhibited by IFN- γ . Suppressive functions of IL-4 include an antagonistic effect on IL-2, and *in vivo* IL-4 appears to have an antitumor effect by enhancing host-mediated immune mechanisms (78).

Interleukin-5 (IL-5)

IL-5 was described as a T-cell-derived mediator enhancing IgA synthesis by B cells and was therefore originally named "T-cell-replacing factor" (TRF). It induces IgM, IgG, and IgE; stimulates the growth of activated normal B cells or B-cell lymphomas; augments some IL-4-induced effects such as IgE synthesis and Fc ϵ -receptor expression; and induces functional receptors for IL-2 on B cells (21). In separate studies, IL-5 has been shown to stimulate the proliferation of eosinophilic precursors, as well as the activity of eosinophils *in vitro*. Recently, the IL-5 receptor was characterized; it is composed of two subunits with different affinities termed the α - and β -chains. The β -chain is shared by the IL-3 and GM-CSF receptor (109).

Interleukin-7 (IL-7)

IL-7 was first isolated from bone-marrow-culture-derived stroma cells (42). However, both human and murine keratinocytes recently were found to release IL-7 (43). It is a growth factor for precursor B cells, induces T-cell IL-2 production and IL-2-receptor expression, and stimulates the proliferation, cytotoxic activity, and generation of cytotoxic T cells, as well as lymphokine-activated killer (LAK) cells (5). Receptors binding IL-7 with low and high affinity were detected on lymphoid and myeloid cells and are similar to the extracellular domain of other cytokine receptors (5).

Interleukin-9 (IL-9)

IL-9 is produced by CD4⁺ T cells and originally was described in the murine system as P40, TCGF III, and mast-cell-growth-enhancing activity (MEA) (26). The IL-9 receptor is a 35-kDa protein which was identified on IL-9-dependent T-cell lines (26, 83). IL-9 is a growth factor for T-helper cells and megakaryoblastic leukemic cells, stimulating the development of erythropoietic colonies. In addition, IL-9 is a growth factor for mast-cell lines and stimulates the production of IL-6 (83). It has also been shown to enhance IL-4-induced IgE production by human B

cells (27). Recently, IL-9 transcripts were detected in HTLV-1-transformed human T cells, Hodgkin's lymphomas, and large cell anaplastic lymphomas (83).

Interleukin-11 (IL-11)

IL-11 was originally detected in murine bone-marrow stromal cells, and the human cDNA was cloned from a fibroblast cell line (74, 79). Recently, IL-11 has also been detected in normal human skin (57). IL-11 stimulates T-cell-dependent development of B cells and synergizes with IL-3 in supporting murine megakaryocyte colony formation. In addition to being a lymphopoietic and hematopoietic cytokine, IL-11 stimulates the synthesis of hepatic acute-phase proteins and is identical with a murine adipogenesis inhibitory factor (74, 79). The IL-11 receptor belongs to a family of cytokine receptors which includes the receptors for IL-6, leukemia inhibitory factor, oncostatin M, and ciliary neurotropic factor, which interact with the same signal-transducing receptor, gp130 (76, 118). In preclinical models, IL-11 was found to be effective in the treatment of thrombocytopenia and neutropenia (74).

Interleukin-12 (IL-12)

IL-12 is a heterodimer consisting of two covalently linked chains, p35 and p40, and was initially described as cytotoxic lymphocyte maturation factor (CMLF), or natural killer-cell-stimulating factor (NKSF) (40, 116). In addition to B cells and macrophages, keratinocytes have recently been shown to produce this multifunctional, immunomodulating cytokine (7). IL-12 enhances the cytotoxic activity of T cells, NK cells, LAK cells, and macrophages, as well as their surface molecule and cytokine receptor expression. Moreover, it acts as a synergistic factor for hematopoietic stem cells (19, 111). In addition, IL-12 can selectively induce a Th1-type immune response because it supports the development of Th1 cells from naive T cells (62, 111). Recently, it was found that treatment of Th-cell precursors with IL-12 resulted in a stable priming for IFN- γ . Moreover, established Th2 clones responded to IL-12 with a transient, low-level expression of IFN- γ (61). IL-12 also induces the production of other cytokines such as IL-10 and inhibits IgE secretion (19). A defective production of IL-12 may explain disease states, such as atopy, associated with a predominance of Th2 cells. In animal models, a significant effect of IL-12 against *Leishmania* and *Toxoplasma*, as well as a potent antitumor effect, has been reported (19).

Interleukin-14 (IL-14)

IL-14 is a recently characterized T-cell-derived cytokine, which originally was named high-mol.-wt. B-cell growth factor. Accordingly, IL-14 induces the proliferation of activated B cells and inhibits immunoglobulin secretion by mitogen-stimulated B cells (4).

Interleukin-15 (IL-15)

Recently, a new cytokine that stimulates the proliferation of T cells via interaction with the β -chain of the IL-2 receptor has been isolated and designated IL-15. It is distinct from IL-2 but shares many of the biologic activities of IL-2 and is produced by many different cells (39).

Interferon-gamma (IFN- γ)

IFN- γ is produced by activated T cells of the Th1 type and, unlike IFN- β and IFN- α , has a central role in modulating the immune response. IFN- α and - β share a common receptor, while IFN- γ binds to a distinct molecule (34). IFN- γ inhibits Th2-cell proliferation; upregulates MHC molecule expression on Langerhans' cells, keratinocytes, and endothelial cells; and increases the expression of various types of adhesion molecules on these cells. Furthermore, IFN- γ upregulates cytotoxic T-cell and NK cell functions, and acts as an immunostimulatory cytokine in various types of T-cell-dependent immune responses *in vitro* (33). However, IFN- γ has also been found to induce suppressor-cell formation and to inhibit antigen presentation for both induction and elicitation of CD4+ lymphocyte-dependent, T-cell-mediated immune responses (33, 72). Because of its inhibitory effects on Th2 cells and IgE production, IFN- γ has been used for the treatment of atopic dermatitis with some success (41, 60). In addition to its immunomodulatory functions, IFN- γ is a potent antineoplastic and antiproliferative agent capable of inhibiting the proliferation of fibroblasts and normal and neoplastic keratinocytes, as well as mast cells (33, 34).

Granulocyte/macrophage-colony stimulating factor (GM-CSF)

GM-CSF, like IL-3, is a multilineage CSF which also stimulates the function of neutrophils, eosinophils, and macrophages, and is a growth factor for myeloleukemic cells. Moreover, GM-CSF inhibits the migration of neutrophils; induces phagocytosis, eicosanoid production, and antibody-dependent cytotoxicity (ADCC); and stimulates tumoricidal and antimicrobial effects, as well as cytokine pro-

duction of macrophages (55, 95). The GM-CSF receptor is similar to the IL-3 receptor and is expressed on several myeloid and nonmyeloid cells (109).

GM-CSF production within the skin has been shown both at the mRNA and the protein level in keratinocytes, fibroblasts, mast cells, macrophages, and endothelial cells (100). Upon various stimuli such as antigen or irritant application, IL-1, and UV-irradiation, or during inflammatory skin diseases, keratinocytes respond with enhanced GM-CSF release (95, 100). GM-CSF receptors have been found on epidermal Langerhans' cells, macrophages, and dendritic cells (90). GM-CSF appears to play an important role in cutaneous immunity; it maintains Langerhans' cell viability during short-term *in vitro* culture, but also induces profound alterations of Langerhans' cell function when investigated *in vitro*. It is essential to the ability of epidermal antigen-presenting cells to sensitize naive unprimed T cells, although upregulation of MHC class II molecules on Langerhans' cells during *in vitro* culture appears to be independent of GM-CSF (12, 90). The functional changes of Langerhans' cells induced by GM-CSF can be antagonized by TNF- α (90). Moreover, GM-CSF appears to be involved in immunosurveillance of neoplastic growth, because effective sensitization against tumor antigens was found to be greatly upregulated by GM-CSF (38). In addition to its effects on Langerhans' cells, GM-CSF may also be a growth-promoting factor for other resident or recruited cells within the skin (49).

Cytokines with antiinflammatory activity

Interleukin-10 (IL-10)

IL-10 originally was described as a cytokine which is produced by Th2 cells and which inhibits the release of cytokines by Th1 cells (50). Meanwhile, it became clear that IL-10 is produced not only by T cells, but also by a various other cells, including B cells and keratinocytes (31, 70, 85). IL-10 production in the skin is found to be enhanced upon application of contact allergens, while tolerogens or irritants have no effect (30). Moreover, UVB light upregulates IL-10 production in murine keratinocytes, and there is good evidence that keratinocyte-derived IL-10 is involved in UVB-induced systemic immunosuppression (85, 86). In contrast to human IL-10 (hIL-10), murine IL-10 (mIL-10) is species specific and affects only murine cells (70). Recently, the IL-10 receptors (IL-10R) have been cloned; hIL-10R binds only human IL-10, whereas mIL-10R binds both human and murine IL-10. Because both human and murine IL-10R are structurally related to the IFNR, they belong to the class II subgroup of cytokine receptors (45, 56).

Viral homologues of IL-10 are encoded by the

Epstein-Barr virus (EBV) and the equine herpesvirus type 2. The viral IL-10 (vIL-10), which is encoded by the EBV homologue (BCRF-1), shares some, but not all, biologic effects of IL-10 on mouse and human cells (70, 89). Both IL-10 and BCRF-1 block IFN synthesis, which inhibits the generation and outgrowth of EBV-transformed B cells; thus, EBV may manipulate the immune response to virally infected cells, consequently promoting survival of the virus (71).

IL-10 inhibits the effector functions of Th1 cells; hence, it may play a role in determining the class of immune response directed against the particular antigen in the downregulation of DTH (70, 72). This is further supported by recent findings indicating that IL-10 suppresses the effector phase of CHS (98). Subcutaneous injection of IL-10 before hapten application was found to induce antigen-specific tolerance via inhibition of proinflammatory cytokines such as IL-1, IL-2, TNF- α , IFN- γ , and GM-CSF (32). Moreover, an animal model showed that IL-10 prevents lethality to endotoxin by inhibition of TNF- α secretion (35). Recently, IL-10 was found to be chemotactic for CD8⁺ T cells, but to inhibit IL-8-induced CD4⁺ T-cell migration (48). Moreover, IL-10 costimulates thymocytes and mast cells and inhibits the antigen-presenting function of macrophages and B cells by downregulating MHC class II antigen expression (70). In addition to being a growth and differentiation factor for human B cells, IL-10 also was identified as a switch factor for IgG1 and IgG3 (17). Because IL-10 upregulates the expression of adhesion molecules such as ICAM-1 and ELAM-1 on human dermal microvascular endothelial cells, it appears to be one of the mediators causing leukocyte accumulation in cutaneous inflammatory reactions (77, 112).

Interleukin-13 (IL-13)

IL-13 is a T-cell-derived factor which mainly affects monocyte and B-cell functions. Its action spectrum is similar to that of IL-4 and includes upregulation of MHC class II, CD23, and IL-1RA expression on monocytes and B cells, as well as stimulation of their antigen-presenting function (68, 82). IL-13 also enhances the proliferation of preactivated B cells and directs human B cells to switch to IgG4 and IgE synthesis (119). Moreover, IL-13 was found to inhibit human immunodeficiency virus replication in monocytes (69). Unlike IL-4, IL-13 does not activate human T cells and is less potent than IL-4 in inhibiting IFN- γ production by NK cells. The production of proinflammatory cytokines (IL-1, IL-6, TNF) and chemokines by macrophages and the antibody-dependent cytotoxic activity is downregulated by IL-13 (119). There is recent evidence of

distinct receptors for IL-13 and IL-4, which may share a common subunit (8). These preliminary findings indicate that IL-13, like IL-4 and IL-10, is another T-cell-derived cytokine with potential anti-inflammatory activities. However, further investigations on the *in vivo* effects of IL-13 are required to determine its actual role in immunologic and inflammatory processes.

Transforming growth factor-beta (TGF- β)

The TGF- β family consists of at least five homodimeric polypeptides which can influence diverse biologic processes including cell growth, differentiation, and morphogenesis (63). The major source of TGF- β is activated platelets, but upon stimulation TGF- β is secreted by many different cells, including keratinocytes (66, 87). In addition to its effects on cell growth, TGF- β has proved to be able to influence inflammatory responses; for example, it causes adhesion and chemotaxis of leukocytes, and at higher concentrations it stimulates T cells and monocytes to release inflammatory mediators. TGF- β also promotes T-cell proliferation, is involved in the differentiation of CD4⁺ Th0 into CD8⁺ Th1 cells, and regulates B-cell-antibody production (114).

On the other hand, TGF- β has proved to be crucial in suppressing inflammatory reactions; it inhibits the function of differentiated macrophages and blocks the proliferation of CD4⁺ lymphocytes. TGF- β suppresses IgM and IgG synthesis, but upregulates IgA production. It also inhibits IL-1R expression, induces the synthesis of IL-1RA, and modulates acute-phase protein production. Whether activation or suppression occurs appears to depend on the state of differentiation of a cell (113).

Neuroendocrine hormones

There is increasing evidence that neuroendocrine hormones not only selectively regulate the function of the central and peripheral nervous system, but also influence the activity of various immunocompetent cells (18). Many of these hormones are produced outside the brain by different cells. Within the epidermis, POMC, the precursor of the melanocyte-stimulating hormone (MSH) and adrenocorticotropin (ACTH), was of particular interest. Accordingly, it could be shown that epidermal cells such as melanocytes and keratinocytes release α -MSH and ACTH. The production of these POMC peptides by keratinocytes was upregulated both at the transcriptional and translational level after treatment with IL-1, UV light, or tumor promoters (PMA) (94).

POMC peptides are known to modulate immune and inflammatory reactions (18). Accordingly, α -MSH blocks particular functions of IL-1, i.e., in-

duction of thymocyte proliferation and prostaglandin (PG)_{E2} release by fibroblasts. The ability of either IL-1 or TNF- α to cause fever, leukocytosis, and enhancement of plasma acute-phase proteins was inhibited by the simultaneous administration of α -MSH (20). Moreover, α -MSH reversed the suppressive influences of IL-1 or TNF- α on the effector phase of CHS in animals (88). Recently, α -MSH was also found to downregulate the expression of MHC class I antigens on mononuclear cells, but not to affect class II antigen or ICAM-1 expression (59). In addition, α -MSH also appears to be a stimulator of the activity of NK cells (52).

There is even more evidence of the immunomodulatory ability of POMC-derived peptides because it has been shown that α -MSH inhibits the production of IFN- γ by PBMC (59). Recent findings indicate that α -MSH, in a dose-dependent manner, upregulates the synthesis and release of IL-10 by human PBMC. Most interestingly, only the C-terminal tripeptide of α -MSH appears to be required for its immunomodulating effects (13). Moreover, ACTH seems to be able to modulate IL-4- and anti-CD40-driven release of IgE by PBMC. ACTH at physiologic concentrations increased IgE synthesis, whereas higher doses of ACTH strongly inhibited IgE synthesis by PBMC. Similarly, α -MSH affected human IgE synthesis and also was found to downregulate IFN- γ mRNA synthesis (2). Accordingly, POMC may play a role in the pathogenesis of allergic diseases and may represent the postulated neuroendocrine arm in diseases such as atopic dermatitis.

These findings raise new and important aspects concerning cutaneous inflammation. Because α -MSH can antagonize particular biologic activities of the proinflammatory cytokine IL-1, it may play a crucial role in the downregulation of inflammatory reactions within the skin (59). For more insights into these mechanisms, the signals influencing the release of α -MSH by keratinocytes need to be studied. In particular, the influence of UV irradiation on the release of α -MSH by keratinocytes appears to be relevant, because keratinocytes are the main target of UV light, which is known to cause local as well as systemic immunosuppression. Recently, it was found that epicutaneous application of α -MSH suppresses both the sensitization and elicitation limbs of cutaneous immune response to potent contact sensitizers (84, 88). UV light is well known to suppress the induction of CHS (47). Thus, the UV-induced production of α -MSH by keratinocytes may be involved in mediating the suppressive effect on the epicutaneous sensitization response. This agrees with previous studies in which mediators released from keratinocytes inhibited CHS when injected *i.v.* into test animals (102).

Conclusion

There is now clear evidence of a complex network of interacting mediators including cytokines, hormones, and others which function as crucial regulatory elements in the pathogenesis of skin diseases. Any cell within the epidermis and dermis after appropriate stimulation can release these factors as well as express the respective receptors. Moreover, there is a high degree of redundancy among different cytokines and other mediators because they have overlapping activities and may use similar signal-transducing pathways. Therefore, it is of major importance to elucidate further the cytokine cascade; such elucidation will offer new insights into the pathomechanisms of inflammatory and immune reactions and perhaps will allow the development of new therapies for skin diseases.

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