Cytokine Loops Involving Interferon-γ and IP-10, a Cytokine Chemotactic for CD4+ Lymphocytes: An Explanation for the Epidermotropism of Cutaneous T-Cell Lymphoma?

By Andreas H. Sarris, Teresa Esgleyes-Ribot, Mary Crow, Hal E. Brommeyer, Nikos Karasavvas, William Pugh, Douglas Grossman, Albert Deisseroth, and Madeleine Duvic

Human interferon-γ (IFN-γ)-inducible protein 10 (IP-10), a C-X-C chemokine, is secreted by IFN-γ-stimulated keratinocytes and is chemotactic for CD4+ lymphocytes. We therefore investigated its role in the epidermotropism of cutaneous T-cell lymphoma (CTCL) that is known to express a C-X-C chemokine, is secreted by IFN-γ-stimulated keratinocytes and is chemotactic for CD4+ lymphocytes. We therefore investigated its role in the epidermotropism of cutaneous T-cell lymphoma (CTCL) that is known to express a C-X-C chemokine, is secreted by IFN-γ-stimulated keratinocytes and is chemotactic for CD4+ lymphocytes.

IFN-γ mRNA in the epidermis and is characterized by an indolent course with multiple relapses that remain confined to the skin for many years. By injecting purified recombinant (r) IP-10 we generated a polyclonal rabbit antiserum that specifically recognized and neutralized rIP-10. With immunoperoxidase staining, IP-10 expression was limited to the basal epidermal keratinocytes of normal skin. In biopsies of CTCL lesions the expression of IP-10 was markedly increased and it extended to the suprabasal keratinocytes in 17 of 18 patients, but it was detectable only faintly in the dermal or epidermal lymphoid infiltrates in 2 of these 18 patients. In 1 patient who had matching biopsies performed before and after treatment, IP-10 was overexpressed before treatment, but was normally expressed in the posttreatment biopsy that showed resolution of the CTCL. Increased IP-10 expression was not detected in any of 4 patients with B-cell lymphoma involving the dermis. On the basis of these findings and a review of the literature, we propose that secretion of IFN-γ by the lymphoid infiltrate in CTCL induces the epidermal keratinocytes to secrete IP-10 that, in turn, is chemotactic for CTCL, accounting for its epidermotropism. This model may be used as a basis for future investigations of the pathogenesis of CTCL.

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Cutaneous T-cell lymphoma (CTCL) is an indolent lymphoproliferative disorder, usually preceded by a prolonged premalignant dermatitis. CTCL is almost always a disease of mature postthymic CD4+ lymphocytes that have a cerebriform nucleus and rearranged T-cell antigen receptors. Pathologically, the diagnosis of CTCL is based on the presence of both architectural (band-like lymphoid infiltrate in the upper dermis and sterile Pautrier's microabscesses in the epidermis) as well as cytological atypia (malignant infiltrating lymphocytes with cerebriform nuclei). Mycosis fungoides designates CTCL involving the skin with patches, plaques, and tumors and Pautrier's microabscesses, whereas Sezary syndrome designates CTCL with malignant cells in the peripheral blood in association with generalized erythroderma and variable degrees of cutaneous infiltration by malignant lymphocytes. However, conservative measures, such as topical alkylating agents, ultraviolet light, low-dose methotrexate, and spot radiotherapy, or a combination of intensive chemotherapy and total skin electron-beam radiotherapy can induce remissions that are not durable in most patients. The disease usually remains limited to the skin for many years and extends to lymph nodes and viscera or transforms to large-cell lymphoma only late in its natural history.

We were intrigued by the report that the epidermis of human CTCL lesions express mRNA for interferon-γ (IFN-γ), which, in turn, can induce keratinocytes to secrete IFN-γ-inducible protein-10 (IP-10). Because IP-10 is chemotactic for human CD4+ lymphocytes, we investigated its role in the pathogenesis of CTCL.

Human IP-10 was cloned as an IFN-γ-inducible cDNA from U-937 cells but was also induced in vitro in many cell lines by lipopolysaccharide, tumor necrosis factor (TNF-α), IFN-γ, interleukin-1α (IL-1α), and IL-6. In vivo administration of TNF-α or IFN-γ induced expression of IP-10 in skin or microglia. IP-10 belongs to the chemokine family that includes small secreted basic proteins of approximately 7 to 10 kD. The family was so named because of the activating and chemotactic properties of its members towards neutrophils, monocytes, and lymphocytes. The chemokines are divided into two subfamilies by the arrangement of the first two of four conserved cysteines that are adjacent in the C-C or β subfamily but are separated by one amino acid residue in the C-X-C or α subfamily. The latter, in addition to IP-10, includes β-thromboglobulin (β-TG), GRO-α, IL-8, neutrophil-activating peptide 2 (NAP-2), macrophage inflammatory protein (MIP)-2α, and MIP-2β, whose genes are clustered on human chromosome 4q12-21. The chemokines exert their actions by binding to specific serpentine cell-surface receptors coupled to G-proteins, but the steps following receptor binding have not yet been completely elucidated.

Initial studies suggested that secreted IP-10 migrated with an apparent size of 6 to 7 kD on sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and was not immunoprecipitated with an antiserum raised against a...
synthetic peptide corresponding to the 22 carboxy-terminal residues of its predicted sequence. This finding led to a hypothesis that IP-10 was secreted after removal of the signal sequence and also after additional proteolytic removal of approximately 22 residues from the carboxy-terminal end.6

By expressing defined fragments of IP-10 in Escherichia coli we showed that inaccurate estimates of molecular weight accounted for the previously reported size of IP-10 that migrates on SDS-PAGE with an approximate size of 10 kD. Furthermore, we showed with immunoprecipitation and Western blotting that the antiserum raised against the 22 carboxy-terminal residues recognized both natural and recombinant (r) IP-10. We suggested that the previous results could be explained by inadequate exposure of the cognate epitopes because of insufficient IP-10 denaturation. We concluded that naturally occurring IP-10 was secreted after removal of the signal sequence without any detectable post-translational processing of the carboxy-terminal end and contained amino acid residues 22 to 98 of the predicted sequence. We designated the natural form of IP-10 as f(22-98), and by expression and purification in E. coli, we showed that it included early subsets of human hematopoietic progenitors.16 Human IP-10 corresponding to f(22-98) was chemotactic for human monocytes and CD4+ lymphocytes17 but was inactive for neutrophils.18,19 The chemotactic activity of IP-10 may account its in vivo antitumor activity.20

We now report our immunocytochemical investigation of IP-10 expression in CTCL lesions and propose a model in which a cytokine loop consisting of IFN-γ, secreted by lymphocytes, and IP-10, secreted by epidermal keratinocytes, may explain the epidermotropism of CTCL.

MATERIALS AND METHODS

Human rIP-γ-γ was a gift from Dr G. Garotta (Hoffman-LaRoche, Basel, Switzerland). Human recombinant granulocyte-macrophage colony stimulating factor (rGM-CSF), rIL-3, and steel factor (rSLF) were gifts of the Immunex Corp (Seattle, WA). Human rMIP-1α, rMIP-1β, rMCP-1, rMCP-2, rMCP-3, rRANTES, rIL-8, rGRO-α, and rC-10 were generous gifts of Dr Dennis Taub (National Cancer Institute, Frederick, MD). Human IP-10 was purified from baculovirus or E. coli as previously described.16

AS522 is a polyclonal antiserum generated by immunizing rabbits with f(22-98) purified from E. coli.16 Recombinant protein (500 μg) was emulsified with complete Freund’s adjuvant and injected intra-dermally in rabbits with booster injections of 250 μg in incomplete Freund’s adjuvant every 2 weeks. Antibodies were detected by enzyme-linked immunosorbent assay (ELISA) using purified f(22-98) and a method described for MIP-1α.21 Titers were defined as the serum dilution giving half-maximal color development in ELISA. Biotinylated goat antirabbit IgG, streptavidin peroxidase, and 3,3′-diaminobenzidine, and the sections were then counter stained with Mayer’s hematoxylin and photographed through a Nikon light microscope (Nikon, Inc, Melville, NY). Negative control reactions for the specificity of staining included incubation with nonimmune rabbit serum or omission of the immune serum. Positive control for the presence of protein in the sections was staining with antibodies for type I transglutaminase.1,22

RESULTS

We generated a polyclonal rabbit serum (AS522) against IP-10 by expressing and purifying from E. coli rIP-10 that was indistinguishable from natural IP-10. Western blotting showed that this antisem reacted only with IP-10 from supernatants of normal epidermal keratinocytes (Fig 1), thus excluding the possibility that the subsequent immunoperoxidase staining reflects staining with antibodies against minor human proteins contaminating the rIP-10 preparation. Specificity of AS522 for IP-10 was also confirmed with ELISA, for which its titer was 3,000 (results not shown) and for which, at a dilution of 1/1,000, AS522 recognized native rIP-10 but not rMIP-1α, rMIP-1β, rMCP-1, rMCP-2, rMCP-3, rRANTES, rIL-8, rGRO-α, or rC-10 (Fig 2). The ability of AS522 to specifically recognize native rIP-10 was also shown by neutralization of the suppressive activity of rIP-10 in the hematopoietic progenitor colony assay (Fig 3). Addition of rIP-10 to low-density marrow cells did not affect the number of CFU-GM generated by plating with rGM-CSF. The addition of rSLF to rGM-CSF doubled the number of colonies, and under these conditions rIP-10 caused a dose-dependent reduction in CFU-GM. Maximum inhibition reduced the CFU-GM number to that obtained by plating with...
Fig 1. Antiserum AS522 detects secretion of IP-10 by primary normal keratinocytes. Keratinocytes were cultured in the presence of 0, 50, 250, and 500 U/mL of IFN-γ. After 24 hours, the supernatants were collected, concentrated with 10% trichloroacetic acid, and processed for Western blotting with AS522 diluted 1,000-fold as described. The numbers to the right side of the figure are the molecular weights in kilodaltons located at the sites of migration of the marker proteins. BV indicates purified recombinant baculovirus IP-10 that, as shown previously, commigrates with f(22-98), indicating secretion of IP-10 after removal of the signal sequence but without any other posttranslational modification.

rGM-CSF alone. Preincubation of control medium with excess AS522 had no effect on colony formation, but preincubation of medium containing rIP-10 with excess AS522 abolished the inhibitory effect of rIP-10 (Fig 3). Even under conditions of antibody excess, AS522 did not recognize rIL-8, rPF4, or rMIP-1α because it did not affect their inhibitory activity in the hematopoietic progenitor assay.

The subjects of this study were 18 previously untreated patients with CTCL whose clinical characteristics are shown in Table 1. No patient was seropositive for human immunodeficiency virus 1/2 or for human T-cell lymphotropic virus I/II. Clinical evaluation showed stage I in 6, stage II in 5, stage III in 1, and stage IV in 6 patients. Biopsies of CTCL lesions showed a band-like infiltrate in the upper dermis in 18 patients and epidermotropism over the malignant lymphoid infiltrate but not uninvolved skin in 17 patients. All 6 patients with stage IV disease had circulating Sezary cells and erythroderma, but they all also had dermal lymphoid infiltrates as well as involvement of the epidermis with Pautrier’s microabscesses. No patient in our series had primary erythrodermic Sezary syndrome with circulating malignant cells without cutaneous dermal and epidermotropic lymphoma.

Immunohistochemical staining of normal skin with AS522 showed that IP-10 expression was limited to basal keratinocytes (Fig 4A), as previously reported. There was no staining in the absence of primary serum or with nonimmune rabbit serum (data not shown). Staining of biopsy samples from the CTCL lesions showed increased expression of IP-
infiltrate (Fig 4E, small arrowheads) but was normal in intensity in the epidermis immediately overlying the malignant lymphoid infiltrates of only 2 of 18 patients with CTCL. Remission-inducing therapy eliminated most malignant lymphocytes and normalized the IP-10 expression in areas of prior cutaneous lesions. The overexpression of IP-10 appeared to be specific for CTCL, because it was not seen in the biopsies of 4 patients with B-cell lymphoma involving the dermis.

Based on previously formulated models for the trafficking of lymphocytes,26,27 we propose a model in which epidermal keratinocytes, benign or malignant lymphocytes, and cytokine loops involving IFN-γ and IP-10 play pivotal roles in the pathogenesis of CTCL (Fig 5). This model includes three sequential and partly overlapping steps. First, skin-homing T lymphocytes return to skin by binding of the cutaneous lymphocyte-associated antigen (CLA)39 to E-selectin39 that is expressed in skin in delayed hypersensitivity40 and chronic inflammation49 that often precede CTCL. The second step, ie, lymphocyte activation, occurs when keratinocyte-secreted IP-10 binds to cell-surface receptors and activates lymphocytes, causing their migration to the epidermis. Lymphocyte activation is associated with conformational changes on their cell-surface integrins that mediate the third step, ie, their strong binding to intercellular adhesion molecules (ICAMs) on keratinocytes, and cause the subsequent lymphocyte retention in the epidermis. These three steps would result in the formation of the sterile Pautrier’s microabcesses characteristic of CTCL. The focal overexpression of IP-10 over CTCL lesions strongly suggests that a diffusible inducer of IP-10 is secreted by either the malignant or the reactive lymphocytes of the lymphoid infiltrate. We suggest that this factor is IFN-γ, which induces keratinocytes to secrete IP-10 and also express ICAMs, thus enabling them to attract and to retain CD4+ lymphocytes in the epidermis. We cannot specify whether IFN-γ is secreted by the malignant or the reactive lymphocytes of the lymphoid infiltrate. We suggest that this factor is IFN-γ, which induces keratinocytes to secrete IP-10 and also express ICAMs, thus enabling them to attract and to retain CD4+ lymphocytes in the epidermis. We cannot specify whether IFN-γ is secreted by the malignant or the reactive lymphocytes of the lymphoid infiltrate. We suggest that this factor is IFN-γ, which induces keratinocytes to secrete IP-10 and also express ICAMs, thus enabling them to attract and to retain CD4+ lymphocytes in the epidermis. We cannot specify whether IFN-γ is secreted by the malignant or the reactive lymphocytes of the lymphoid infiltrate. We suggest that this factor is IFN-γ, which induces keratinocytes to secrete IP-10 and also express ICAMs, thus enabling them to attract and to retain CD4+ lymphocytes in the epidermis. We cannot specify whether IFN-γ is secreted by the malignant or the reactive lymphocytes of the lymphoid infiltrate. We suggest that this factor is IFN-γ, which induces keratinocytes to secrete IP-10 and also express ICAMs, thus enabling them to attract and to retain CD4+ lymphocytes in the epidermis.

Table 1. Clinical Characteristics of the Patients With CTCL and Results of Immunoperoxidase Staining of Their Cutaneous Biopsies for IP-10

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Stage</th>
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<th>Malignant Lymphocytes</th>
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<td>−</td>
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<td>II A</td>
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Patients no. 12 through 18 had involvement of the peripheral blood and cutaneous patches, plaques, or tumors and epidermotropism. All immunoreactivity reported here is the result of staining with AS522 diluted 200- to 400-fold in different experiments.

DISCUSSION

We used purified bacterial rIP-10 to generate a polyclonal rabbit antiserum that recognized denatured and native rIP-10 but not other chemokines, especially RANTES, MCP-1, MIP-1α, and MIP-1β, that are chemotactic for T lymphocytes.50 Immunoperoxidase staining showed qualitative and quantitative differences in IP-10 expression between CTCL and normal skin. The IP-10 expression was higher in CTCL where it extended to the suprabasal keratinocytes overlying the lymphomatous infiltrates. Even though IP-10 can be secreted in vitro from monocytes and activated lymphocytes,51 it was detected in the malignant lymphocytes of only 2 of 18 patients with CTCL. Remission-inducing therapy eliminated most malignant lymphocytes and normalized the IP-10 expression in areas of prior cutaneous lesions. The overexpression of IP-10 appeared to be specific for CTCL, because it was not seen in the biopsies of 4 patients with B-cell lymphoma involving the dermis.

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dermal IFN-γ mRNA was detected in all 7 patients with epidermotropic CTCL but only in 1 of 3 patients with Sezary syndrome. Epidermal keratinocytes from patients with CTCL secrete both unidentified inducers of IL-1α and also IL-1α, which itself is an inducer of IP-10. LFA-1 and ICAM-1 are required for the binding of T lymphocytes to IFN-γ–treated keratinocytes and were detected in the epidermis of epidermotropic CTCL but not in the epidermis of 2 patients with Sezary syndrome without epidermotropism. Purified peripheral blood T lymphocytes from these 2 patients bound to normal epidermis only after preincubation of the latter with IFN-γ. This finding was interpreted by the investigators as the result of ICAM-1 induction in epidermal keratinocytes by IFN-γ. However, exposure of

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\text{Fig 4. Immunoperoxidase staining of IP-10 in frozen sections from skin biopsies of CTCL lesions. (A) Normal skin. (B, C, D, and E) CTCL lesions. (F) Follicular small cleaved cell B-cell lymphoma involving the dermis. (A), (B), and (C) were photographed with a 10 x; (E) and (F) with a 4 x; and (D) with a 40 x objective, respectively. The arrows mark the location of the Pautrier's microabcesses (B, C, and D), and the large arrowheads mark the location of the malignant lymphocytes under the keratinocytes with increased IP-10 staining that are marked with the small arrowheads. Note that the epidermis distant from the band-like malignant lymphoid infiltrate stains normally for IP-10 (E).}
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keratinocytes to IFN-γ would also induce secretion of IP-10, and the resulting activation of the malignant lymphocytes would enable them to bind to ICAM-1.38

Our 6 patients with Sezary syndrome had circulating malignant cells and simultaneously had epidermotropism and overexpression of IP-10 in the lesional epidermis. This finding can be explained by the coexistence of two malignant cell populations in our patients with Sezary syndrome, ie, the epidermotropic cells form the skin lesions and the circulating cells. The existence of two populations was previously suggested,4 but it remains unclear whether they represent two separate compartments or whether malignant cells can move from the circulating to the epidermotropic compartment. Our model suggests testable hypotheses for the generation of the nonepidermotropic population. These hypotheses include chemokine receptor mutation or deletion, as suggested by the profound leukocytosis caused by knock-out of the murine IL-8 receptor homologue.41 Other possibilities include deficient postreceptor signaling, deficient expression of integrins, and an altered cytokine secretion pattern that renders the circulating cells unresponsive to chemotactic signals originating from the epidermis. In fact the circulating CD4+ lymphocytes purified from the peripheral blood of patients with Sezary syndrome had mRNAs for IL-4, IL-5, and IL-10 but not for IFN-γ,4,31,42 and this deficiency in IFN-γ secretion could not be overcome by phytohemagglutinin or phorbol esters.42

This model explains both the epidermotropism of malignant lymphocytes and their preferential localization in the epidermis.39 Combined with the demonstration that most epidermal but few dermal lymphocytes are proliferating,43 it also suggests that the epidermotropism is essential for the growth of CTCL and may explain the repeated cutaneous relapses and lack of initial clinical visceral dissemination in patients with Sezary syndrome. It also provides a framework to explain the therapeutic effects of cyclosporin-A and interferons in CTCL. As reported, even when the lymphoma responds, it always relapses shortly after the discontinuation of cyclosporin-A, regrows rapidly to the pretreatment volume, and then slows down to its previous pace.44 Because cyclosporin-A is cytostatic, it may act by inhibiting IFN-γ production by T cells45 and eliminating the inducer of IP-10. It is likely that, after the discontinuation of cyclosporin-A treatment, the synthesis of IFN-γ resumes, the cytokine loops are reestablished, and the malignant lymphocytes rapidly return to the epidermis explaining the appearance of very rapid tumor regrowth that paradoxically slows down once it reaches its pre-cyclosporin-A bulk. IFN-α or IFN-γ, both active against CTCL,46 can, at low concentrations, induce but, at higher concentrations, suppress the induction of IP-10 mRNA in U-937 cells.3 This dose-dependent effect of interferons provides a way to override the inductive effect of IFN-γ on the synthesis of IP-10 by keratinocytes. Abolition of the epidermotropic IP-10 signal by either interferons or cyclosporin-A might lead to redistribution of CTCL to other visceral sites in the body, away from the epidermis where they divide,43 and thus explain the observed therapeutic effects. The role played by the infiltrating reactive lymphocytes and by IP-10 in the host response to CTCL is undefined. Because only small amounts of IP-10 are rarely detectable in the lymphocytes of CTCL lesions, it probably does not mediate an antitumor response against CTCL as it did in immunocompetent mice challenged with syngeneic tumors that secreted high amounts of IP-10.40

This model, developed in response to data presented here and reported in the literature, emphasizes that active participation of both keratinocytes and benign or malignant lymphocytes is important for the pathogenesis of CTCL. Thus, it provides a framework for the systematic investigation of the roles played by IP-10 (and possibly other chemokines), selectins, integrins, and adhesion molecules in the biology of CTCL. We hope that a more detailed understanding of the pathogenesis, growth control mechanisms, and clinical evolution of CTCL will help in the identification of new therapeutic agents with novel mechanisms of action. Possible candidates are peptides or antibodies capable of blocking chemokine-receptor binding or molecules that inhibit signal transduction after chemokine-receptor binding. Novel therapeutic agents are clearly needed because, at present, there is no curative treatment for most patients with CTCL.

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REFERENCES


32. Nickoloff BJ, Lewinsohn DM, Butler EC, Krenskey AM, Clayberger C: Recombinant gamma interferon increases the binding of peripheral blood mononuclear leukocytes and a Leu-3+ T lymphocyte clone to cultured keratinocytes and to a malignant cutaneous squamous carcinoma cell line that is blocked by antibody against the LFA-1 molecule. J Invest Dermatol 90:17, 1988


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