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Oncostatin M Secreted by Skin Infiltrating T Lymphocytes Is a Potent Keratinocyte Activator Involved in Skin Inflammation

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Cutaneous inflammatory diseases such as psoriasis vulgaris and atopic dermatitis are associated with altered keratinocyte function, as well as with a particular cytokine production profile of skin-infiltrating T lymphocytes. In this study we show that normal human epidermal keratinocytes express a functional type II oncostatin-M (OSM) receptor (OSMR) consisting of the gpl30 and OSMRβ components, but not the type I OSMR. The type II OSMR is expressed in skin lesions from both psoriatic patients and those with atopic dermatitis. Its ligand, OSM, induces via the recruitment of the STAT3 and MAP kinase pathways a gene expression profile in primary keratinocytes and in a reconstituted epidermis that is characteristic of proinflammatory and innate immune responses. Moreover, OSM is a potent stimulator of keratinocyte migration in vitro and increases the thickness of a reconstituted epidermis. OSM transcripts are enhanced in both psoriatic and atopic dermatitic skin as compared with healthy skin and mirror the enhanced production of OSM by T cells isolated from diseased lesions. Results from a microarray analysis comparing the gene-modulating effects of OSM with those of 33 different cytokines indicate that OSM is a potent keratinocyte activator similar to TNF-α, IL-1, IL-17, and IL-22 and that it acts in synergy with the latter cytokines in the induction of S100A7 and β-defensin 2 expression, characteristic of psoriatic skin. Taken together, these results demonstrate that OSM and its receptor play an important role in cutaneous inflammatory responses in general and that the specific effects of OSM are associated with distinct inflammatory diseases depending on the cytokine environment.


The skin is a large and complex tissue providing a protective interface between the organism and its environment. The epidermis forms the regenerating outer surface of the skin and consists of multiple layers of specialized epithelial cells, the keratinocytes. In response to stress or injury, keratinocytes release signaling molecules that modulate the expression of cell surface receptors and modify their cytoskeleton morphology, thereby altering their proliferative and migratory capacities. These changes are closely associated with an inflammatory response that leads to either wound healing or defense against microbial infection, and often leading to chronic disease. Among the most common inflammatory skin diseases in the Western population are psoriasis vulgaris and atopic dermatitis. Although the mechanisms underlying their pathogeneses are different, both disorders are associated with keratinocyte hyperplasia, proliferation, and altered differentiation as well as with the presence of increased numbers of T cells in the lesions secreting a wide variety of cytokines. It is generally accepted that immune responses in atopic dermatitis are associated with the activity of cytokines secreted by Th2 lymphocytes that contribute to the high IgE levels and eosinophilia characteristic of this condition. In contrast, the immune response in psoriasis is mediated by Th1 and most likely by Th17 cells (1) that secrete inflammatory cytokines and are furthermore associated with local neutrophil infiltration. Interestingly although both skin diseases are characterized by defective skin barriers, patients with atopic dermatitis, in contrast to those with psoriasis, suffer from frequent serious skin infections (2) that are associated with a particular gene expression profile in epidermal keratinocytes (3).

Oncostatin M (OSM)4 is a member of the IL-6 family of cytokines, which are multifunctional proteins involved in immunity, hemopoiesis, bone modeling, and inflammatory processes. Mainly secreted by activated T cells, monocytes, and dendritic cells, OSM

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4 Abbreviations used in this paper: OSM, oncostatin M; OSMR, OSM receptor; LIF, leukemia inhibitory factor; LIFR, LIF receptor; NHEK, normal human epidermal keratinocyte; RHE, reconstituted human epidermis; CK, cytokeratin; VEGF, vascular endothelial growth factor.
is a proinflammatory mediator that strongly triggers acute phase protein synthesis by liver cells (4, 5). Many of its biological functions are also shared with the leukemia inhibitory factor (LIF), another IL-6 family member. These shared and specific functions of OSM are explained by the existence of two types of OSM receptor (OSMR) complexes. In addition to the common LIF/OSM type I receptor complex composed of the gp130 and LIFR receptor β (LIFRβ) subunits, OSM also specifically recognizes a type II receptor in which the gp130 receptor chain is associated with the OSMR β-chain (6–8). The OSM-induced signaling cascade involves activation of certain Janus kinases (JAK1, JAK2, and Tyk2) and signal transducers and activators of transcription (STAT1 and STAT3), as well as MAPK pathways (9). The OSMR β subunit is mainly expressed by fibroblasts, endothelial, hepatic, lung, and hemopoietic cells, and it has been reported that OSMRβ can be also recruited by IL-31, a recently identified cytokine with skin tropism (10).

In the present study we have determined the expression of both OSMR and OSM in the lesions of cutaneous inflammatory diseases and have investigated the effect of OSM on keratinocytes in vitro and in vivo by analyzing a gene expression profile specifically selected to study keratinocyte structure and function (11). We show that the expression of the type II, but not the type I OSMR, is enhanced in both psoriatic and atopic dermatitic lesions and that OSM-induced, STAT3-mediated keratinocyte alteration is associated with cutaneous inflammatory responses.

Materials and Methods

Cell culture

All of our studies involving human tissues were reviewed and approved by the institutional ethics committee on human experimentation "Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale" of the Région Poitou-Charentes. Normal human epidermal keratinocytes (NHEK) were obtained and cultured as described previously (12). A keratinocyte migration assay was performed as described previously (13). In vitro constituted human epidermis (RHE) was purchased from SkinEthic Laboratories (14). Skin-infiltrating or peripheral blood T cells were expanded using Expander beads (Invitrogen Life Technologies) as described previously (15, 16). For cytokine production, 2 × 10⁶ T cells/ml were activated with immobilized anti-CD3 mAb, anti-CD28 mAb, and IL-2 for 24 h and cytokine production was analyzed by ELISA.

Reagents

Cytokines were purchased from R&D Systems Anti-gp130 (AN-HH1, AN-HH2, AN-G30), anti-OSMRβ (AN-N2, AN-R2, and AN-V2), and anti-LIFRβ (AN-E1) mAbs were produced in the laboratory, and the neutralizing anti-OSMRβ Ab (XR-M70) came from Immuxon. Polyclonal anti-gp130, anti-LIFRβ, anti-STAT3, anti-S100A8, and anti-S100A9 Abs were from Santa Cruz Biotechnology; anti-S100A7 and anti-filaggrin Abs were from Lab Vision. IL-1β, IL-6, IL-8, IL-10, IL-12p70, and TNF-α goat peroxidase-conjugated Ab was from Sigma-Aldrich; and the anti-rabbit peroxidase-labeled Ig were from CliniSciences; rabbit anti-goat peroxidase-conjugated Ab was from Sigma-Aldrich; and the anticytokeratin (CK) 10 and anti-filaggrin Abs were from Lab Vision. IL-1β, IL-6, IL-8, IL-10, IL-12p70, and TNF-α were quantitated using the BD cytometric bead array (BD Biosciences). The detection of OSM, CXCL5, MIP-3β, CCL17, and vascular endothelial growth factor (VEGF) was conducted using ELISA kits bought from R&D Systems.

Flow cytometric and immunohistochemical analyses

For flow cytometric analyses, cells were incubated with the appropriate primary mAb (AN-G30, AN-N2, or AN-E1) or with an isotype control mAb followed by incubation with a PE-conjugated anti-mouse mAb and analyzed using a BD Biosciences flow cytometer. For immunohistochemical analysis, 10-μm cryostat sections were fixed, permeabilized, and immunostained with the relevant primary Ab (AN-R2) and the avidin peroxidase method (Vector Laboratories). Sections were counterstained with Mayer’s hematoxylin (Sigma-Aldrich) before mounting.

Gene expression profiling using cDNA arrays

Poly(A)⁺ RNA enrichment and hybridization to custom Atlas array membranes displaying 600 cDNAs (11) were performed according to the manufacturer’s recommendations (Clontech Laboratories) as previously described (12).

A study of the effects of 33 cytokines on the overall expression of 154 genes of potential interest for skin physiology was performed using keratinocyte designed cDNA microarrays (17).

Quantitative RT-PCR analysis

cDNA was synthesized from 2 μg of total RNA using random hexamer primers. Quantitative RT-PCR was conducted using the LightCycler FastStart DNA MasterSYBR Green I kit (Roche) and the following primers: gp130 (forward 5’-CCGCCACATAATTTATCAGT-3’ and reverse 5’-AAGGTCTTGGACAGTGAATG-3’); OSMRβ (forward

FIGURE 1. Type II OSM receptor expression and OSM-induced signaling pathways in NHEK. A, Quantitative RT-PCR analysis was conducted on total RNA from six independent NHEK cultures. gp130, OSMRβ, and LIFRβ mRNA expression levels are shown relative to the housekeeping GAPDH mRNA. B, Flow cytometric analysis of gp130, OSMRβ, and LIFRβ expression on NHEK. The dark gray histograms correspond to the isotype control Ab binding and the light gray histograms to the detection of gp130, OSMRβ, or LIFRβ, respectively. C, Western blot was performed on immunoprecipitated NHEK lysate using anti-gp130, anti-OSMRβ, or anti-LIFRβ Abs. The GO-G-UVI glioblastoma cell line was used as a positive control. D, NHEK were stimulated for 15 min in the presence or absence of the indicated concentrations of OSM. Phospho-STAT3 (P-STAT3) and STAT3 protein levels were determined by Western blotting. E, Cells were incubated for 2 h in the presence of 15 μg/ml neutralizing anti-gp130 and anti-OSMRβ mAbs or an isotype control Ab before a 15-min stimulation with 50 ng/ml OSM. P-STAT3 and STAT3 were immunodetected as in D. F, NHEK were stimulated for 15 min with or without 50 ng/ml OSM or LIF. P-STAT3 and STAT3 were immunodetected as in D. G, Phospho-ERK (P-ERK) and ERK protein levels were analyzed by Western blotting in response to a 50 ng/ml OSM stimulation.
5'-AGATTGAACTCCATGGTGAA-3' and reverse 5'-GCTTCAAGTGTGGTGAAGTT-3'; LIFR (forward 5'-TCTTGCGAGCCTATACAGAT-3' and reverse 5'-TCTGGATTTGGAATATCAGG-3'); S100A7, S100A8, and S100A9 (12), -defensin 2 (forward 5'-GCCATCAGCCATGAGGGTCTTG-3' and reverse 5'-AATCCGCATCAGCCACAGCAG-3'); filaggrin (forward 5'-AGGAACAGGCAAGGTCAAGTCCAG-3' and reverse 5'-CACGTGTGAACTCTTGGTGGCTCT-3'); OSM (forward 5'-TCAGTCTGGTCCTTGCACTC-3' and reverse 5'-CTGCAGTGCTCTCTCAGTTT-3'); and GAPDH (forward 5'-GAAGGTGAAGGTCGGAGTC-3' and reverse 5'-GAAGATGGTGATGGGATTTC-3') and hydroxymethylbilane synthase (12) as housekeeping genes.

Western blotting analysis

For STAT3 and MAPK phosphorylation and β-tubulin expression, NHEK were lysed in SDS sample buffer, submitted to SDS-PAGE, transferred onto an Immobilon membrane, and stained with the appropriate Ab. The reaction was visualized by chemiluminescence. To determine the expression of the gp130, LIFR, and LIFRβ chains, cells were lysed in Brij 96 lysis buffer as described previously (18). Samples were subsequently incubated overnight with the indicated mAbs (AN-G30, AN-V2, or AN-E1), and the complexes were isolated using protein A beads before being treated as described above. Analysis of S100A7, S100A8, and S100A9 protein expression was conducted as previously described (12) on NHEK cultured in the absence or presence of OSM.

Results

Human keratinocytes express a functional type II OSMR on their surface

We first studied the expression profile of the type I and type II OSMR by NHEK by analyzing the expression levels of transcripts for the gp130, LIFRβ, and OSMRβ chains. NHEK, established from six different healthy donors, predominantly expressed transcripts for OSMRβ and gp130, whereas only very faint levels of LIFRβ mRNA were detected (Fig. 1A). In agreement with these results, NHEK were found to express both the gp130 and OSMRβ chains, but no LIFR β subunit, at their cell surfaces as shown by flow cytometric and Western blotting analyses (Fig. 1, B and C).

Engagement of a functional OSMR results in activation of STAT3, and therefore we analyzed the capacity of OSM to induce the activation of this signaling pathway in NHEK. As shown in Fig. 1D, stimulation of NHEK with OSM strongly induced tyrosine phosphorylation of STAT3. The addition of either a neutralizing anti-gp130 or an anti-OSMRβ mAb to the cultures before OSM stimulation resulted in decreased STAT3 phosphorylation (Fig. 1E), indicating that both of the subunits defining the type II OSMR are involved in OSM-mediated STAT3 activation in keratinocytes. In contrast, stimulation of NHEK with LIF, at concentrations ranging from 3 to 100 ng/ml, did not result in STAT3 activation (Fig. 1F and data not shown).

Because signaling via the type II OSMR complex is also known to recruit the MAPK pathway (19), we measured ERK1/2 tyrosine phosphorylation levels in NHEK. Stimulation of NHEK with OSM led to a rapid increase in ERK1/2 phosphorylation levels (Fig. 1G). Taken together, these results demonstrate that human keratinocytes express a functional type II OSMR complex, but no type I OSMR complex, on their cell surface.
OSM modulates the expression of genes associated with human keratinocyte function

We next analyzed the keratinocyte gene expression profile and its regulation by OSM using macroarrays composed of cDNAs that were specifically designed to study keratinocyte structure and function (11). The results depicted in Fig. 2 are based on the analysis of transcripts expressed by NHEK, as well as by RHE following a 24-h stimulation with OSM. In both models OSM upregulated the expression of 34 and 22 genes, respectively, following a 24-h stimulation with OSM or without 10 ng/ml OSM. In a quantitative RT-PCR analysis of S100A7 mRNA expression was performed. Results are expressed as the relative expression of stimulated cells over control cells. NHEK were cultured with or without 10 ng/ml OSM and a quantitative RT-PCR analysis of S100A7 mRNA expression was performed. NHEK were cultured with or without 10 ng/ml OSM for 48 h and a quantitative RT-PCR analysis of S100A7 mRNA expression was performed. C, NHEK were cultured with or without 10 ng/ml OSM for 48 h and a quantitative RT-PCR analysis of S100A8, S100A9, β-defensin 2, and filaggrin mRNA expression was performed. D, NHEK were cultured with or without 10 ng/ml OSM for 48 and 96 h. S100A7, S100A8, and S100A9 protein levels were determined by Western blotting. E, IL-8, CXCL5, and VEGF concentrations were determined by ELISA or cytometric bead array analysis in RHE culture supernatants after a 48-h stimulation with or without 10 ng/ml OSM.

OSM is a potent inducer of keratinocyte migration and triggers hyperplasia of the reconstituted human epidermis

Keratinocytes play an important role in both the pathogenesis of cutaneous inflammatory diseases and the wound-healing process. We therefore analyzed the functional effects of OSM on human keratinocytes by using an in vitro wound-healing model, based on the induction of keratinocyte migration, in which proliferation is inhibited. As shown in Fig. 4, OSM strongly enhanced the motility of NHEK to a similar extent as that induced by epidermal growth factor, which is known to promote the migration of keratinocytes and was used as a positive control (13).

To extend these observations to a more dynamic model of epidermal differentiation, we investigated the effects of OSM on basal cell layer proliferation and keratinocyte differentiation using a reconstituted human epidermis. RHE grown in the absence of OSM presented a keratinized, multistratified epithelium containing intact
basal, spinous, granulous, and cornified cell layers and numerous keratohyalin granules in the upper granular layer (Fig. 5). The addition of OSM to RHE triggered hyperplasia of the spinous keratinocyte layer, leading to an increase in the overall thickness of the reconstituted tissue. This effect was accompanied by a decrease of keratohyalin granules in the granular layer as well as by the presence of pyknotic nuclei. OSM-treated RHE were further characterized by an enhanced expression of S100A7, as well as a down-modulation of filaggrin and CK10 expression (Fig. 5), in agreement with the gene expression profile induced by OSM (Fig. 2).

Both type II OSMR expression and OSM production are enhanced in inflammatory skin diseases

Because OSM was found to be a potent inducer of keratinocyte motility and to trigger hyperplasia of RHE, suggesting its potential role in the pathogenesis of inflammatory skin disorders, we determined the expression of the OSMR β-chain in psoriatic and atopic dermatitic lesions by immunohistochemical analysis. Lesions of both pathologies were characterized by a thickened epidermis, a decreased stratum granulosum, parakeratosis, and a strong up-regulation of S100A7 expression. In addition to the ubiquitous expression of gp130 (data not shown), the OSMR β-chain was highly expressed in lesions from both psoriatic and atopic dermatitic skin, as compared with healthy tissue (Fig. 6A).

Moreover, both psoriatic and atopic dermatitic lesions contained elevated levels of OSM mRNA, in contrast to biopsies taken from healthy skin where the expression of these transcripts was undetectable (Fig. 6B). To determine whether T cells infiltrating cutaneous inflammatory sites are a source of OSM, T cells were isolated from skin biopsies, expanded for 10–12 days in culture, and subsequently analyzed for their capacity to produce OSM. T cells isolated from the cutaneous lesions of patients with psoriasis or atopic dermatitis or derived from the peripheral blood of psoriatic patients produced higher levels of OSM following activation than peripheral blood-derived T cells from healthy individuals (Fig. 6C). Taken together, our results demonstrate that T cells infiltrating inflammatory skin lesions are important sources of OSM and therefore may contribute, via the induction of keratinocyte inflammation, to skin pathology.

OSM is one of the major cytokines involved in keratinocyte activation and differentiation

Skin inflammation results from the action of a cytokine network in which OSM is only a single player among many. To more precisely define the contribution of OSM to this process, its capacity
to modulate the expression of keratinocyte inflammatory, innate immunity, and differentiation gene profile was compared with that of a comprehensive series of 33 cytokines, using microarray analysis.

The results from this extensive analysis showed that only few cytokines, i.e., IL-1α and β, IL-6, IL-17, IL-20, IL-22, IL-24, and TNF-α, were able to induce a gene expression profile in NHEK cells. Relative S100A7 and β-defensin 2 mRNA expression was determined by quantitative RT-PCR analysis. Results are expressed as the relative expression of stimulated cells as compared with control cells. CNTF, Cardiotrophin-like cytokine; NP, neuropoietin; and TSLP, thymic stromal lymphopoietin. Relative S100A7 and β-defensin 2 mRNA expression was determined by quantitative RT-PCR analysis. Results are expressed as the relative expression of stimulated cells as compared with control cells.

We next analyzed in detail the contribution of the most potent cytokine from each cytokine subfamily to the induction of S100A7 and β-defensin 2 gene expression by quantitative RT-PCR analysis. The combined effects of IL-1α, IL-17, IL-22, TNF-α, and OSM at a suboptimal concentration of 1 ng/ml led to a strong synergistic induction of the expression of analyzed genes (Fig. 7B). Furthermore, by successive elimination, IL-17, TNF-α, and OSM were identified as the major response-inducing cytokines (Fig. 7B). Finally, by using in vitro RHE we confirmed that, similarly, the combination of IL-17, TNF-α, and OSM led to a strong synergistic induction of S100A7 and β-defensin 2 mRNA expression when compared with the action of each cytokine alone (Fig. 7C).

**Discussion**

Psoriasis and atopic dermatitis are the most frequent cutaneous inflammatory disorders affecting the population in Western countries. Although they differ in their origin, it is generally accepted that the pathogenesis of each of these diseases is associated with immune responses implicating the activity of T cells that reside in cutaneous inflammatory sites (20). In particular, the production by these cells of various set of cytokines is involved in the activation, proliferation, and hyperplasia of keratinocytes that are characteristics of the chronic cutaneous inflammation observed in these disorders.

In the present study, we show that OSM secreted by skin-infiltrating T cells is capable of modulating the expression of a large number of genes involved in keratinocyte function. These OSM-induced effects are mediated specifically via the type II OSMR, composed of the gp130 and OSMRβ chains, which is, in contrast to the type I OSMR, functionally expressed on keratinocytes from healthy skin, thereby extending a recent report in the literature (21). Moreover, the expression of the OSMR-chain transcripts is strongly enhanced both in cutaneous lesions from patients with psoriasis or atopic dermatitis as compared with that in normal skin, suggesting an up-regulation of type II OSMR expression under conditions of cutaneous inflammation.

As shown in the present and previous studies, the interaction of the type II OSMR with its ligand results in the activation of the STAT3 pathway (22). The critical role of the STAT3 signaling pathway in the regulation of pathologic skin immune responses and, in particular, the pathogenesis of psoriasis has been well documented. Keratinocyte-specific ablation of STAT3 in a conditional transgenic mouse model was shown to lead to impaired skin remodeling because of a decrease in the growth factor-induced migration of keratinocytes (13). Moreover, transgenic mice expressing a constitutively active form of STAT3 in keratinocytes develop skin lesions resembling those of human psoriasis (23). It is of note that the induction of this particular phenotype in these transgenic mice not only requires activated STAT3 in keratinocytes but also their interaction with activated T cells, underscoring the importance of T cell-mediated immunity. Our observation that OSM-mediated signaling in human keratinocytes involves the activation of the STAT3 pathway and that the expression of both type II OSMR and OSM are increased in psoriatic lesions suggests that this cytokine might play a role in certain aspects of the pathogenesis of this disease in humans. During the reviewing process of the present work, a related study describing the importance of OSM in the induction of psoriasis-associated genes was published (24). Both studies underline a putative role for OSM in psoriasis. In contrast, the enhanced expression of type II OSMR and OSM in the lesional skin of patients with atopic dermatitis and the production of OSM by T cells isolated from these lesions indicate that OSM is likely to have a broader function in skin inflammation.
Indeed, among the predominant gene products induced by OSM in the cultures of primary keratinocytes and in the reconstituted epidermis are S100A7, also known as psoriasin, and S100A8 and S100A9, which belong to a family of small calcium-binding proteins with inflammation-inducing properties (25). The relevance of the induction of members of the S100 family of proteins by OSM in cutaneous inflammation is furthermore corroborated by the observation that S100A7, S100A8, and S100A9 are detected only at very low levels in the epidermis of healthy donors, whereas their expression is strongly induced in keratinocytes from psoriatic and atopic dermatitic lesions (26, 27).

Both S100A8 and S100A9 have chemotaxis-inducing activity and are strong chemoattractants for neutrophils (28). Moreover, OSM induces the production of IL-8 and CXCL5 by keratinocytes, known to mediate the chemoattraction of the latter cells via CXCR2 (29–31). Because cellular infiltrates in psoriatic contain large numbers of neutrophils (32) that are present in the so-called Munro’s microabscess, these results indicate that OSM, via its effect on keratinocytes, might be involved in leukocyte chemotaxis to these inflammatory skin lesions, thereby contributing to the local cutaneous inflammation.

Keratinocytes from psoriatic patients also produce high levels of antimicrobial peptides (3, 33). These peptides, present only at negligible levels in normal skin, are essential in the cutaneous innate immune response to invading microorganisms, as shown in animal models of infection (34). They might be, at least partially and independently of the bacteriocidal activity of neutrophils, responsible for the lesser susceptibility of psoriatic patients to infections with microorganisms, as compared to patients with atopic dermatitis who frequently suffer from serious skin infections. In particular, S100A7 has been shown to confer resistance to infection of the skin by Escherichia coli (35). Similarly, β-defensin 2, another protein with anti-microbial activities (36) induced by OSM in human keratinocytes, is expressed at high levels in psoriatic lesions (37). The lower antimicrobial peptide production observed in atopic dermatitic skin, despite the increased expression of the type II OSMR and its ligand, could be a result of the concomitant increased production of IL-4, IL-10 and IL-13 in these patients, which have previously been described as inhibitors of β-defensin 2 synthesis (3, 38).

As reported previously, transcripts for several STAT3-signaling cytokines, including IFN-γ, IL-6, and the IL-10-related cytokines IL-19, IL-20, and IL-22, are increased in psoriatic lesions (17, 39, 40). In addition, a number of cytokines that do not activate STAT3 following interaction with their respective receptors, such as IL-1, IL-17, and TNF-α, are also overexpressed in psoriasis (39, 41, 42), suggesting their implication in this disease. By comparing the capacity of a large series of cytokines to modulate the expression of genes associated with keratinocyte-mediated inflammation, chemotaxis, and innate immune responses, we found that among the STAT3-signaling cytokines OSM is one of the most potent mediators of keratinocyte activation. Moreover, by using combinations of IL-1α, IL-17, IL-22, TNF-α, and OSM, as well as successive subtractions of the latter cytokines, we were able to determine that IL-17, TNF-α, and OSM are important mediators in the induction of a subset of keratinocyte gene products associated with skin inflammation. The combination of these three cytokines leads to a very strong synergy with maximal values of gene induction of 10² to 10⁴-fold at higher concentrations of cytokines.

Taken together, the results of our study demonstrate that OSM is one of the very few T cell-derived cytokines that is able to directly trigger keratinocyte activation via the recruitment of the STAT3 pathway. Because T cell infiltrates are a major source of OSM, this cytokine, together with an increased expression of its receptor components in both psoriatic and atopic dermatitic skin, may participate to the phenotype and tissue remodelling observed in these inflammatory skin diseases. Finally, our data show that OSM and its receptor play an important role in cutaneous inflammatory responses in general, whereas its specific effects associated with distinct inflammatory diseases depend on the cytokine environment.

Disclosures

The authors have no financial conflict of interest.

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