Keratinocytes as targets for interleukin-10-related cytokines: a putative role in the pathogenesis of psoriasis

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ABSTRACT. **Cytokines are key factors in the cross talk between the immune system and other systems including hepatic, nervous, cardiac and cutaneous systems, leading to an adaptive and integrated response of the organism to stress. They are also involved in the regulation of many processes, including hematopoiesis, the immune response and inflammation. IL-10 is one of the most important anti-inflammatory cytokines. Five cytokines structurally related to IL-10 have been described and presently form this family of cytokines: IL-19, IL-20, IL-22, IL-24 and IL-26. In contrast to IL-10, these cytokines display pro-inflammatory activities in different tissues, including skin. Indeed, some of them induce an inflammatory keratinocyte gene expression profile and an epidermis histology resembling psoriatic lesions. In this review, we discuss recent knowledge about the effects of cytokines of the IL-10 family on keratinocytes and their potential role in psoriasis, a cutaneous inflammatory disease.**

Keywords: cytokines, skin, keratinocyte, inflammation, psoriasis

Cytokines induce and control hematopoiesis, as well as immune and inflammatory responses. They are also key factors in the cross talk between the immune system and other systems including hepatic, nervous, cardiac and cutaneous systems, leading to an adaptive and integrated response of the organism to stress. The regulation of cytokine production is essential for homeostasis, and a dysregulation of cytokine production can lead to the development of pathologies. Th1 cells, through their production of interferon γ (IFN-γ), are critical for the eradication of intracellular pathogens, but can also cause inflammatory pathologies. Th2 cells by contrast, are important for the regulation of responses to parasites, but the associated production of interleukin (IL)-4, IL-5 and IL-13 can promote allergic manifestations. Cytokines directing Th1 and Th2 responses, produced by the respective T cell subsets, have been shown to cross-regulate each other's development and function. Regulatory T cells represent another subpopulation of T lymphocytes with immunosuppressive properties that mainly produce transforming growth factor β (TGF-β) and IL-10 and are involved in the generation and maintenance of immune tolerance.

Effective immune responses against pathogens are sometimes accompanied by strong inflammatory reactions. To minimize damage to self, the activation of the immune system al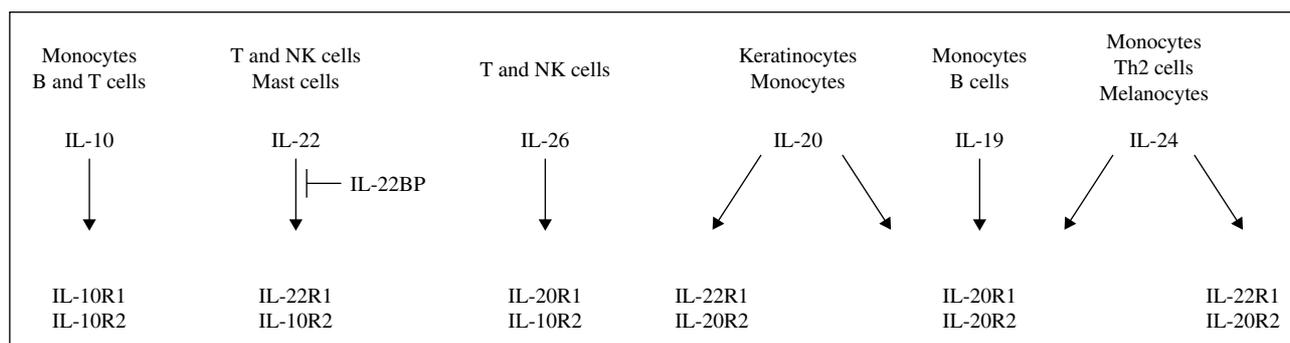so triggers anti-inflammatory processes. Both inflammatory and anti-inflammatory reactions are normal components of the immune response, which fight infections while preventing immune pathology. Among the anti-inflammatory cytokines, IL-10 is one of the most important and is produced by a large number of immune cells.

In this review, we will discuss current knowledge about the effects of the IL-10 family of cytokines on keratinocytes and the cutaneous system, and their potential role in psoriasis.

IL-10-RELATED CYTOKINES

IL-10 was identified in 1989 as a "cytokine synthesis inhibitory factor", and its biological activities are now well defined [1, 2]. Since 1995, five cytokines, structurally related to IL-10, have been described and presently form this family of cytokines: IL-19, IL-20, IL-22, IL-24 (melanoma differentiation-associated gene mda-7) and IL-26 (AK-155) [1, 3-9]. They are mainly produced by immuno-hematopoietic cells and act through heterodimeric receptors belonging to the type II cytokine receptors family *(figure 1)*.

IL-10 mediates its biological activities through the IL-10R1/IL-10R2 receptor [10-12]. The IL-10R2 chain is also a component of the IL-22 receptor, together with the IL-

Monocytes B and T cells	T and NK cells Mast cells	T and NK cells	Keratinocytes Monocytes	Monocytes B cells	Monocytes Th2 cells Melanocytes
IL-10	IL-22	IL-26	IL-20	IL-19	IL-24
	⊣ IL-22BP				
↓	↓	↓	↙ ↘	↓	↙ ↘
IL-10R1 IL-10R2	IL-22R1 IL-10R2	IL-20R1 IL-10R2	IL-22R1 IL-20R1 IL-20R2 IL-20R2	IL-20R1 IL-20R2	IL-22R1 IL-22R1 IL-20R2 IL-20R2

Figure 1
IL-10-related cytokines, cellular sources and receptors.

22R1 subunit [5, 13], and of the IL-26 receptor, in association with the IL-20R1 chain [14]. In contrast to the other subunits, IL-10R2 is ubiquitously expressed in the organism. Consequently, the spectrum of action of IL-10, IL-22 and IL-26 is restricted by the expression pattern of IL-10R1, IL-22R1 and IL-20R1 chains, respectively. The IL-10R1 subunit is mainly detected in lymphoid tissues and immune cells [2, 15, 16], but a weak expression is also observed in skin, pancreas and liver [15]. IL-22R1 is strongly expressed in pancreas and, at lower levels, in skin, colon, small intestine and liver, whereas it is not detected in immuno-hematopoietic cells [15, 17-19 and unpublished results].

The sharing of one or two receptor subunits is frequent in this family of cytokines. Indeed, IL-19, IL-20 and IL-24 act through the IL-20R1/IL-20R2 receptor [4, 20]. IL-20 and IL-24 also bind the IL-22R1/IL-20R2 complex [8, 20, 21]. Although IL-20R1 and IL-20R2 subunits are all expressed in skin, pancreas and liver, only weak expression of IL-20R2 has been detected in immune cells, and IL-20R1 not at all [15, 16, 22].

The common use of receptors subunits explains, in part, the induction of the same signaling pathways. Indeed, the binding of IL-10-related cytokines to their receptors activates the Janus kinase (JAK) and signal transducers and activator of transcription (STAT) pathway; in particular STAT3 [4, 11, 13, 20, 23-25]. IL-22 and IL-24 have also been reported to activate the MAP-kinase pathway [26-28].

Mainly produced by monocytes, macrophages, B and T cells, IL-10 is a multifunctional cytokine with diverse effects on most hematopoietic cells [2]. It inhibits the antigen-presentation capacity of macrophages and dendritic cells (DC) [29-32], and the proliferation of CD4$^+$ T cells [33, 34]. IL-10 strongly inhibits cytokine production such as IL-2 synthesis by T cells [35] and the synthesis of the pro-inflammatory cytokines IL-1β, IL-6, tumor necrosis factor α (TNF-α), monocyte inflammatory protein-1α (MIP-1α), RANTES, IL-8 and eotaxin by monocytes/macrophages [36, 37]. In addition, IL-10 also increases the expression by activated monocytes of several anti-inflammatory proteins, such as IL-1 receptor antagonist, soluble TNF-α receptor and tissue inhibitor of matrix metalloproteinases [2]. These properties contribute to the immunosuppressive and anti-inflammatory activities of IL-10. In contrast, it stimulates Th2 cell differentiation *via* the inhibition of IFN-γ secretion by activated T cells [38]. This cytokine also directly activates B cells proliferation and differentiation, promotes the switch toward IgG1,

IgG3, and in combination with TGF-β, toward IgA1 and IgA2 [2].

In contrast to the anti-inflammatory functions of IL-10, other IL-10-related cytokines are mostly described for their pro-inflammatory activities.

IL-19 is produced by resting and LPS- or granulocyte macrophage-colony stimulating factor-activated monocytes and, at lower level, by B cells [3, 15]. IL-19 induces inflammatory responses by stimulating the expression of IL-6 and TNF-α in monocytes. It also induces the apoptosis of mouse monocytes and the production of reactive oxygen species [39]. IL-19 has also been reported to promote Th2 responses. In human peripheral blood mononuclear cells (PBMC) stimulated with concanavalin A, IL-19 increases IL-4, IL-5, IL-10, IL-13 and IL-19 secretion, and decreases those of IFN-γ [40-42]. It also up-regulates the expression of keratinocyte growth factor (KGF) transcripts by CD8$^+$ T cells [43]. High IL-19 serum levels are observed in patients with asthma as compared to healthy controls, suggesting a role in the pathogenesis of asthma [42].

IL-20 is produced by keratinocytes, glial cells and activated monocytes [4, 15, 44], and was first described for its pro-inflammatory activity in skin [4]. IL-20 stimulates the expression of KGF transcripts by CD8$^+$ T cells [45], increases formation of multipotential hematopoietic progenitor cells [46] and inhibits angiogenesis through the COX-2 regulatory pathway [47].

IL-22 is mainly expressed by activated T cells, mast cells and NK cells [6, 15]. Despite initial controversy, neither resting nor activated immune cells express the IL-22R1 chain, which explains why IL-22 has no effect on hematopoietic cells [5, 15, 18, 48]. IL-22 is involved in the regulation of inflammation in several tissues, including liver [49], pancreas [50], intestine [19] and skin [17, 48], where it up-regulates the expression of pro-inflammatory proteins. In rheumatoid arthritis, IL-22 induces the proliferation of synovial fibroblasts and the production of monocyte chemoattractant protein-1 (MCP-1) by these cells, thereby promoting inflammatory responses [51]. In contrast, IL-22 has a protective effect in murine models of liver injury. Moreover, IL-22 overexpression in the human hepatocellular carcinoma HepG2 cell line promotes cell survival and growth, via the activation of STAT3 [52]. These biological activities of IL-22 are antagonized by the IL-22 binding protein (IL-22BP) soluble receptor, which binds IL-22 and prevents its interaction with the membrane receptor [53-55]. IL-22BP mRNA is expressed by monocytes, activated B cells and epithelial cells. Tissue expres-

sion studies showed a high expression of IL-22BP mRNA in placenta, spleen, skin, and lung, and at lower levels in heart, pancreas and prostate [55].

IL-24 was originally identified as mda-7, a molecule strongly up-regulated following differentiation of the human melanoma cell line HO-1 [7, 8]. This cytokine is expressed by melanocytes [7], by PBMC activated with concanavalin A [8, 15, 56], phytohaemagglutinin [56] or IL-4 and LPS [57], and by some differentiation inducer-treated tumor cell lines [58]. IL-24 induces growth arrest or apoptosis of a large panel of cancer-derived cells, without affecting normal cells [27, 59-65] and as IL-20, inhibits angiogenesis [66]. Interestingly, its expression is inversely correlated with melanoma progression [59, 67]. IL-24 is currently in human Phase I/II clinical trials as a potential anti-cancer drug, through adenovirus-mediated gene therapy [68, 69]. Intratumoral injection of an adenovirus containing the IL-24 gene in patients with advanced cancer results in elevated IL-24 expression and tumor cells apoptosis [68, 69]. IL-24 also activates IL-6, TNF-α and IFN-γ production by PBMC, suggesting its involvement in inflammation [56].

First designated as AK155, IL-26 was cloned as a protein expressed by herpes virus saimiri-transformed T cells [9]. IL-26 is also expressed by activated NK and T cells, particularly type 1 cells [15]. The only IL-26 activity described so far is the induction of IL-8 and IL-10 secretion by the Colo205 carcinoma cell line [14].

INVOLVEMENT OF THE IL-10-RELATED CYTOKINES IN SKIN BIOLOGY

Recently, a growing number of reports have described the implication of IL-10 and its related cytokines in the biology and function of the skin.

IL-10

IL-10 appears to be implicated in the regulation of the cutaneous inflammatory response of wound healing. IL-10 expression is rapidly up-regulated after skin incision [70, 71]. It inhibits the infiltration of neutrophils and macrophages in the injured tissue and down-regulates the expression of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) and chemokines (MCP-1, MIP-1α) [71]. Despite preliminary results suggesting a direct action of IL-10 on keratinocytes, the lack of IL-10R1 expression and STAT3 phosphorylation in response to IL-10 suggest an indirect effect on these cells. This is reinforced by the absence of any biological effect of IL-10 on unstimulated or stimulated normal human epidermal keratinocytes or on the HaCat keratinocyte cell line [17, 72-75].

IL-10 is produced by skin-infiltrating activated T cells (unpublished results), but there are controversial data concerning IL-10 synthesis by keratinocytes. Some studies showed that IL-10 production by keratinocytes depends on the differentiation state and is induced by ultraviolet radiation *in vitro* and *in vivo* [76-78]. In contrast, we and other groups failed to detect any IL-10 mRNA in epidermal

keratinocytes or in the HaCat cell line [79, 80]. In any case, IL-10 expression is up-regulated in skin samples from Th2 pathologies such as atopic dermatitis, melanoma and lymphomas [81-83], whereas a relative deficiency is found in psoriasis, a Th1 disease [84]. These data suggest that IL-10 may indirectly down-regulate keratinocyte inflammatory responses and may thus participate in the regulation of the skin immune network.

IL-20

Skin appears to be a main target for IL-20. Overexpression of IL-20 in transgenic mice causes neonatal lethality with skin abnormalities, including a thickened epidermis, hyperkeratosis and compact stratum corneum, indicating an aberrant epidermal differentiation [4]. The expression of cytokeratin (CK)5, CK6 and CK14, associated with keratinocyte proliferation, is increased. However, the expression of the differentiation markers filaggrin and loricrin are not altered. These perturbations appear to be caused by circulating IL-20, since the same phenotype is observed in mice expressing the transgene in skin, and also in liver and the lymphoid lineage. In the HaCat cell line, IL-20 stimulates the activation of STAT3 and induces the expression of genes involved in inflammation, such as TNF-α, S100A8 and MCP-1 [4].

IL-22

Epidermal keratinocytes, as well as the keratinocyte cell lines HaCat and SVK14, express the two chains of the IL-22 receptor, *i.e.* the IL-10R2 and IL-22R1 subunits [17, 48], whose expression is up-regulated by IFN-γ, but not IL-4 [48]. The binding of IL-22 to its receptor induces the phosphorylation of STAT3 in these cells [17, 48]. Using a cDNA array screening approach, we have demonstrated the involvement of IL-22 in skin inflammatory processes [17]. In epidermal keratinocytes, IL-22 up-regulates, in a dose- and time-dependent manner, the expression of S100A7-psoriasin, S100A8 and S100A9 transcripts, known for their pro-inflammatory activities. Interestingly, the expression of these proteins is up-regulated in psoriasis [85]. Moreover, IL-22 strongly induces the hyperplasia of *in vitro* reconstituted human epidermis, resulting mostly from an inhibition of keratinocyte differentiation. Indeed, IL-22 down-regulates the expression of CK10, involucrin, loricrin and filaggrin, all associated with keratinocyte differentiation, whereas it has no effect on keratinocyte proliferation. Finally, IL-22 induces keratinocyte migration in an *in vitro* wound-healing model [17].

In parallel, Wolk *et al.* showed that in epidermal keratinocytes, IL-22 up-regulates, in a time- and dose-dependent manner, the expression of human β-defensin 2 and β-defensin 3 mRNA, but not that of β-defensin 1. This induction depends on keratinocyte differentiation since an elevated calcium concentration promotes the IL-22-induced β-defensin expression [48]. In addition, IL-22 induces the transcription of S100A7-psoriasin [17, 48], recently shown to confer resistance to skin infection by *Escherichia coli* [86]. High levels of IL-22 are associated with strongly up-regulated β-defensin expression in skin from patients with psoriasis and atopic dermatitis [48].

These data suggest that IL-22 is a T cell-derived cytokine that promotes the cutaneous innate immune response and plays an important role in skin inflammatory processes.

IL-19, IL-24 and IL-26

Normal epidermal keratinocytes express the IL-20R1, IL-20R2, IL-10R2 and IL-22R1 receptor chains, suggesting that they could be a potential target for IL-19, IL-24 or IL-26. In the HaCat cell line, the phosphorylation of STAT3 in response to IL-24 or IL-26, together with an increased secretion of IL-8 in response to IL-26, have been reported [8, 24, 87], suggesting a role for these two cytokines in skin inflammatory responses. Furthermore, the expression of the c49a gene, which exhibits high homology with IL-24, is increased during wound repair in rat [88]. Finally, no biological activities of IL-19 have been reported on keratinocytes so far.

Taken together, these data show that keratinocytes are potential targets for the cytokines of the IL-10 family, except for IL-10 itself. In order to compare the biological activity of these IL-10-related cytokines in the same *in vitro* assay, we performed microarray analysis on cytokine-stimulated normal human epidermal keratinocytes. A differential gene expression profile between cytokine-treated and control cultures is shown in *figure 2A*. In these culture conditions, IL-22 was able to modify the expression of 9 genes out of 154, as compared to 6 for IL-24, 2 for IL-20 and 0 for IL-10, IL-19 and IL-26. This was confirmed by real-time RT-PCR experiments, where IL-22 and, to a lesser extent, IL-24 and IL-20 are shown to down-regulate the expression of the CK10 gene (a differentiation marker) and up-regulate those of the S100A7 gene (an inflammation marker) and the β-defensin 2 gene (an innate immunity marker) *(figure 2B)*. As expected, IL-10 had no effect on epidermal keratinocytes. Finally, IL-19 and IL-26 did not significantly modify the keratinocyte gene expression profile analyzed in our experiment. In agreement with these results, we showed that IL-22, IL-24, and, to a lesser extent, IL-20, are able to induce STAT3 phosphorylation in epidermal keratinocytes *(figure 2C)*. This is of great interest since STAT3 has been shown to be important for skin homeostasis [89, 90]. A weak STAT3 activation is observed in response to IL-19 and IL-26, whereas IL-10 has no effect. The study of the receptor subunit expression showed that normal epidermal keratinocytes express IL-22R1, IL-10R2 and IL-20R2 mRNA, whereas IL-20R1 mRNA is only weakly detected in all three keratinocyte samples tested *(figure 2D)*. Taken together, these results could explain the limited effect of IL-19 and IL-26 on STAT3 activation and suggest that IL-20 and IL-24 act mainly through the IL-22R1/IL-20R2 receptor in epidermal keratinocytes.

The observations that some IL-10-related cytokines induce in keratinocytes a gene expression profile and a morphology resembling psoriatic lesions, together with the human psoriasis-like phenotype of transgenic mice expressing a constitutive active form of STAT3, led us to consider the putative role of these cytokines in the pathophysiology of psoriasis.

IL-10-RELATED CYTOKINES AND PSORIASIS

### Psoriasis: an auto-immune-mediated disease

Psoriasis is one of the most common cutaneous inflammatory pathologies, affecting 2.5 % of the world's population. The cause of psoriasis is still unknown, but seems to result from both genetic predispositions and environmental factors (stress, infections...). Plaque-psoriasis is the most widespread clinical type of this disease and is characterized by scaling, reddened and indurated skin lesions derived from excessive growth of skin epithelial cells [91]. Psoriasis is a cell-mediated disease characterized by a thickened epidermis resulting from a hyperproliferation and an abnormal differentiation of keratinocytes, accompanied by vascular hyperplasia and inflammatory immune cell infiltrates at the lesion site. The pathogenesis of this disease depends on the activation of immune cells, including T cells, DC, neutrophils, macrophages, mast cells, and on the increased production of pro-inflammatory mediators such as cytokines, chemokines and growth factors [92]. Immune cells infiltrated within psoriatic skin secrete large amounts of type 1 cytokines, such as IFN-γ and TNF-α, which play a primary role in the pathogenesis of psoriasis [93]. TNF-α is mainly produced by lesional DC, macrophages and T cells that enhance local inflammation, DC activation and maturation [94]. IFN-γ, produced by both CD4^{+} and CD8^{+} T cells, has a major role in psoriasis too, since subcutaneous injection of IFN-γ has been shown to induce psoriasis in normal skin at the injection site in 10 out of 42 psoriatic patients [95]. Moreover, IFN-γ and TNF-α induce keratinocytes to release pro-inflammatory cytokines such as IL-6, IL-7, IL-8, IL-12, IL-15, IL-18 and TNF-α [96]. Other cytokines highly expressed and potentially involved in psoriatic pathogenesis are IL-1, IL-8, IL-15, IL-18 and IL-12 family members [97-101]. In contrast, nil or low expression of IL-4 and IL-10 Th2 cytokines has been reported in psoriatic lesions [102, 103]. Participating in the recruitment of immune cells to the skin during inflammation are chemokines produced by keratinocytes and/or by inflammatory infiltrates, such as CCL4, CCL17, CCL20, CCL22, CCL27 and CXCL10 [104, 105]. The increased expression of growth factors such as TGF-α, KGF and vascular endothelial growth factor may contribute to changes in angiogenesis [94, 106].

This immune cellular infiltrate, accompanied by a complex network of cytokines, chemokines and growth factors, leads to abnormal keratinocyte proliferation and differentiation as well as altered angiogenesis.

Cytokines of the IL-10 family and psoriasis

Involvement of IL-10 in psoriasis development

In the context of a biased Th1/Th2 balance, conflicting data regarding IL-10 expression in psoriasis have been reported. IL-10 mRNA is either undetected or detected at low levels in lesional psoriatic skin [102, 103], but in any case at lower levels than found in atopic dermatitis and mycosis fungoides [84]. Interestingly, conventional anti-psoriatic treatments are associated with enhanced IL-10 and decreased IFN-γ production by PBMC, suggesting that IL-10 may have anti-psoriatic activity [84, 107]. Consequently, therapeutic effects of recombinant IL-10 in pso-
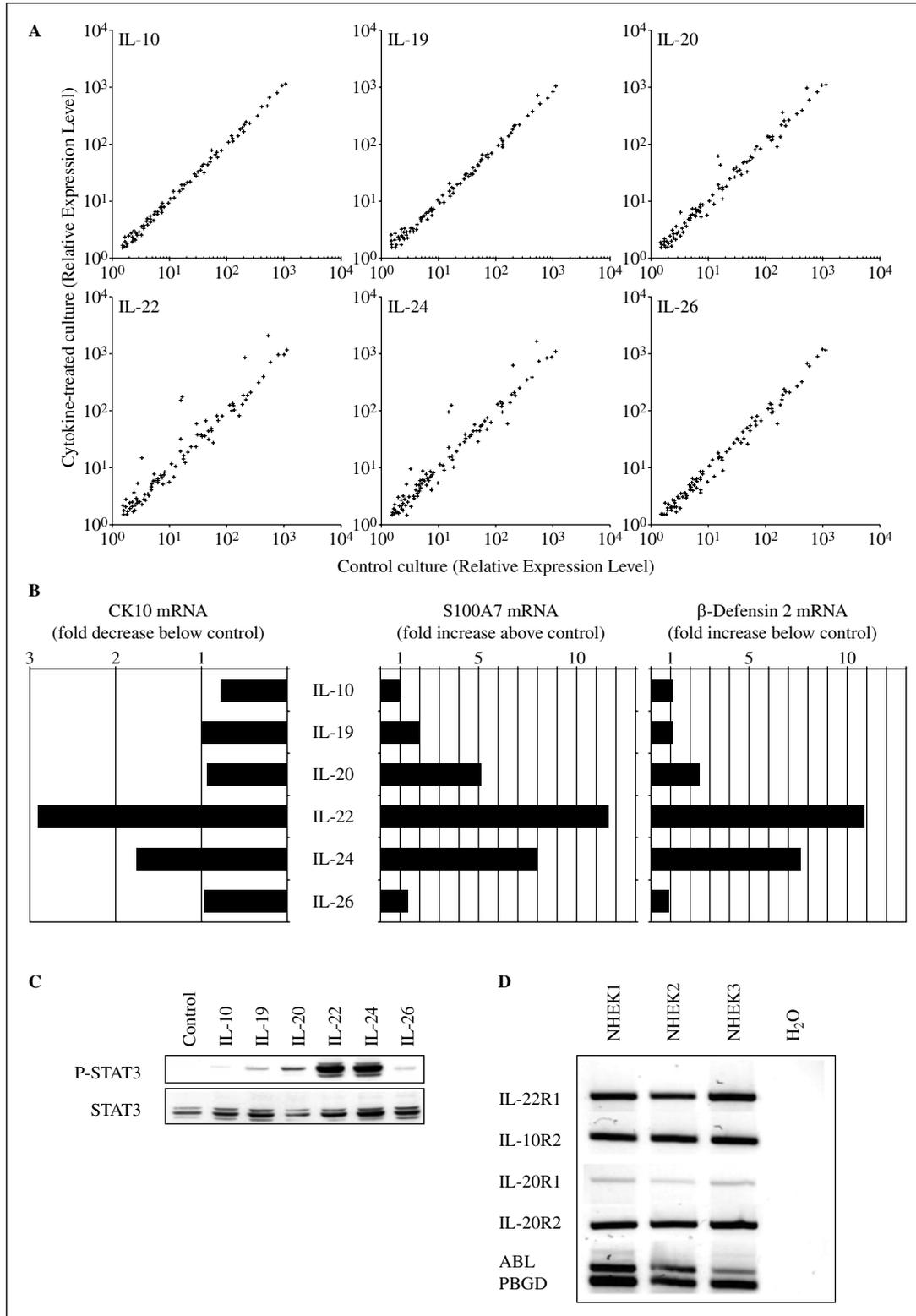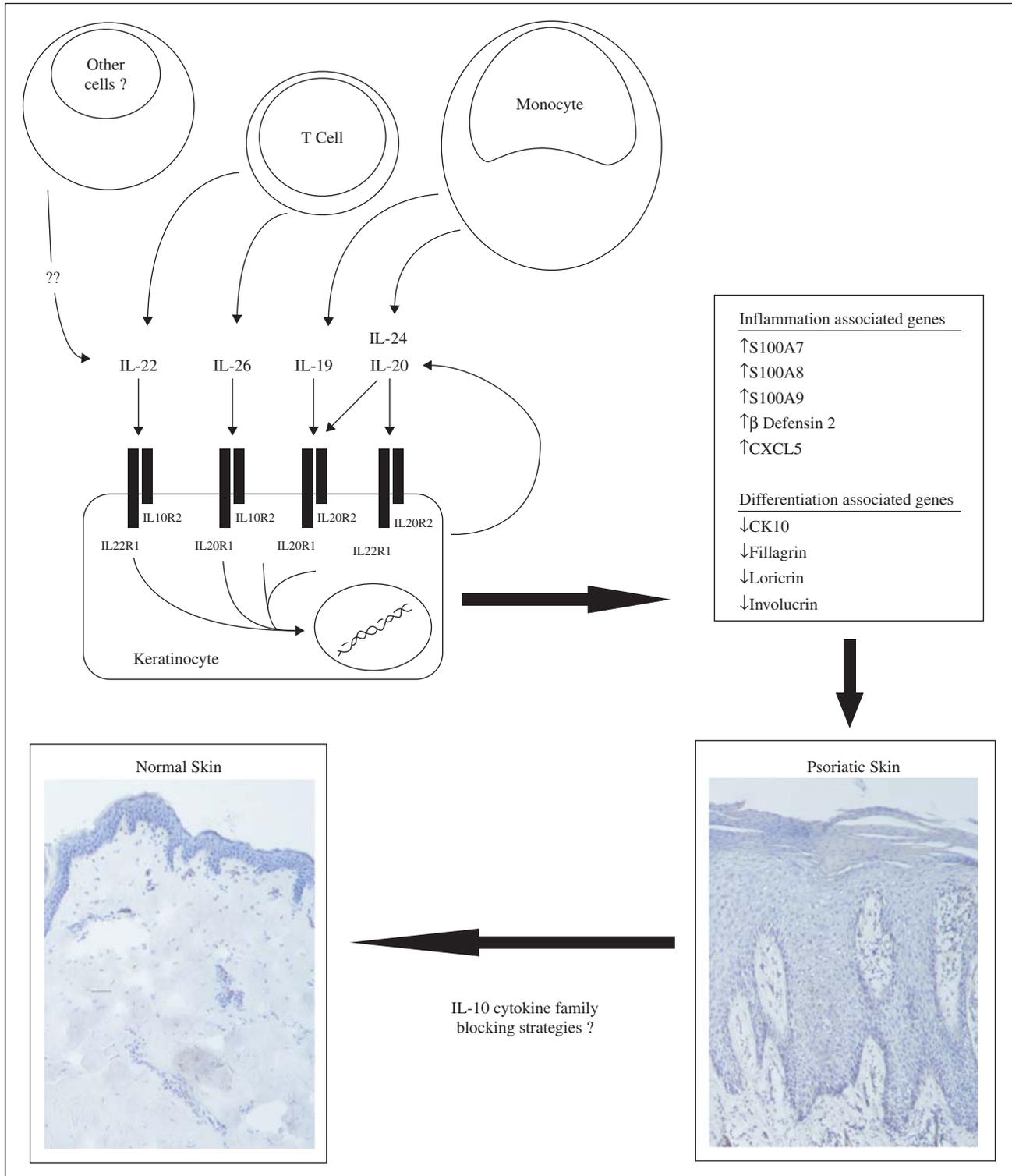
Figure 2

Gene expression profiles and STAT3 activation induced by the IL-10-related cytokines and their receptors expression in epidermal keratinocytes. Normal human epidermal keratinocytes were cultured for 24 h in the presence or absence of 20 ng/ml of IL-10, IL-19, IL-20, IL-22, IL-24 or IL-26. (A) Comparison of the effects of the different cytokines on the overall expression of a panel of 154 genes of potential interest for skin physiology using home-made cDNA microarrays multiplex analysis. After cytokine stimulation, total RNA was extracted and conventional ^{33}P-cDNA target synthesis and hybridization were performed. For each cytokine, the randomized relative expression of each gene is plotted versus that of the corresponding gene from the control culture. (B) Real-time RT-PCR was performed as previously described (17) to determine CK10, S100A7 and β-defensin 2 mRNA relative levels in response to IL-10-related cytokines. (C) Epidermal keratinocytes were stimulated for 30 min with 20 ng/ml of each cytokine. Twenty μg of cell lysate were separated by SDS-PAGE and transferred to a nitrocellulose membrane. Phospho-STAT3 (P-STAT3) and STAT3 protein levels were assessed by Western blot as previously described (17). (D) IL-22R1, IL-10R2, IL-20R1, IL-20R2, Abelson kinase (ABL) and porphobilinogene deaminase (PBGD) mRNA expression in normal human epidermal keratinocytes (NHEK) was detected by RT-PCR.

riatic patients have been studied in several clinical trials. The first pilot trial conducted by Asadullah *et al*. in 1998 showed that subcutaneous treatment with IL-10 leads to a partial or complete disappearance of psoriatic plaque [84]. Phase II clinical trials confirmed that subcutaneous administration of IL-10 is well tolerated and leads to a diminution of the psoriatic area and severity index. In parallel, an improvement of histological parameters, a decreased cutaneous cell infiltration, a decreased lesional expression of IFN-γ, TNF-α, IL-17, IL-8 and CXCR2 and of the systemic type 1/type 2 cytokine ratio have been reported [108, 109]. However, the clinical improvement diminishes after 6 to 8 weeks during the course of a 12-week clinical trial, despite a sustained systemic decrease of type 1 cytokine

Figure 3
Scheme of hypothetical involvement of IL-10-related cytokines in the induction/maintenance of psoriatic phenotype. IL-10-related cytokines induce the expression of genes involved in keratinocyte inflammation and down-regulate the expression of genes associated with keratinocyte differentiation. Taken together, it leads to a phenotype resembling psoriatic skin. These cytokines, together with their receptor subunits, could represent potential targets for the development of new therapeutic strategies.

production [110]. Finally, a phase II clinical trial in patients with chronic plaque psoriasis in remission showed that IL-10 treatment decreased the incidence of relapse [111].

Overall, clinical and biological data generated by these trials demonstrate that IL-10 therapy is well tolerated and is able to target immune cells such as T cells and dendritic cells. The anti-psoriatic activity of IL-10 is likely to be mediated by the impaired antigen presenting properties of DC and/or by the direct inhibition of type 1 cytokine production by Th1 cells. A direct effect of IL-10 on keratinocytes is unlikely since these cells do not express the IL-10R1 chain [17, 73]. However, the expression of the IL-10R2 chain suggests its association with others partners such as IL-20R1, IL-20R2 and IL-22R1 chains, present on keratinocytes, rendering these cells susceptible to the action of IL-19, IL-20, IL-22, IL-24 and IL-26. Since all these cytokines are linked to a pro-inflammatory gene expression profile, their relative involvement in the pathogenesis of psoriasis has been studied.

Expression of the IL-10-related cytokines and their receptors in psoriatic skin

IL-19 and IL-20 mRNA are expressed focally in the epidermis of about 80% of untreated psoriatic patients, and their expression is confined to the basal and suprabasal keratinocyte layers of lesional skin [112]. A careful analysis excluded monocytes/macrophages, lymphocytes, endothelial and dendritic Langerhans cells as sources of IL-19 and IL-20 mRNA. In contrast, IL-24 mRNA is expressed exclusively in the dermal compartment, in mononuclear inflammatory cells. Interestingly, the expression of IL-19, IL-20 and IL-24 mRNA is not detected in non-lesional skin of psoriatic patients [112]. Immunohistochemical studies confirmed that psoriatic skin expresses higher levels of IL-19 and IL-20 protein than healthy skin. However, in contrast to IL-19, whose expression remains confined to basal keratinocytes in psoriasis, IL-20 is over-expressed in the whole psoriatic epidermis [45]. Interestingly, after 4 weeks of treatment with either cyclosporine A or calcipotriol, both IL-19 and IL-20 mRNA disappear, correlating with changes in clinical and histological scores [112]. Such a decrease of IL-19 mRNA expression is also observed in IL-4-treated psoriatic patients, in parallel with a reduced IL-8 production and IFN-γ/IL-4 ratio, whereas IL-20 remains unchanged [113]. These data suggest that IL-19 and IL-20 are keratinocyte-derived pro-inflammatory signal mediators, linked to the presence of autoreactive Th1 cells in psoriatic skin lesion. However, the persistence of IL-20 in IL-4-treated patients suggests that IL-19 and IL-20 expression is differentially regulated in psoriasis.

Based on *in vitro* data, IL-22 also represents a good candidate as a major T cell-derived pro-inflammatory cytokine able to induce a psoriasis-like phenotype. Indeed, Wolk *et al*. and our group reported an increased expression of IL-22 mRNA in lesional skin of psoriatic patients [48 and unpublished results]. Even though skin-infiltrating T cells are good candidates, characterization of the IL-22-producing cells and potential regulation of IL-22 production need to be studied in more details.

In parallel, the expression of the receptors of these cytokines has been studied in psoriatic skin lesions. Blumberg *et al*. first described the up-regulated expression of IL-20R1 and IL-20R2 mRNA in keratinocytes, as well as endothelial and mononuclear cells in psoriatic lesions compared to the very low levels detected in healthy skin [4]. Romer *et al*. confirmed mRNA expression of these receptor chains throughout the psoriatic epidermal layer, whereas IL-22R1 mRNA is predominantly detected in the superficial part of the psoriatic epidermis. A similar, but weaker expression pattern for IL-20R1, IL-20R2 and IL-22R1 chains is detected in uninvolved psoriatic skin [112]. This up-regulated expression of IL-20R1 and IL-20R2 is also observed at the protein level [45]. Interestingly, mRNA levels for IL-20R1, IL-20R2 and IL-22R1 are not affected by cyclosporine A, calcipotriol or IL-4 treatment [112, 113].

Possible relations between the polymorphisms of IL-10, IL-19, IL-20 and IL-24 and psoriasis

Human gene polymorphism has been shown to play a role in immune responses. Some polymorphisms of cytokines and cytokine receptors may have direct functional significance by altering the level of gene expression and/or its function. The relevance of IL-10 gene polymorphisms has been demonstrated in numerous immune inflammatory diseases including rheumatoid arthritis, inflammatory bowel disease and asthma. The positive association of the IL-10.G13 allele with familial psoriasis has been reported, suggesting that the IL-10 locus contributes to the heritability of psoriasis susceptibility [114, 115]. Kingo *et al*. analyzed three single-nucleotide polymorphisms in the IL-10 5′ flanking region in patients with plaque-type psoriasis and in healthy volunteers. The IL-10 ACC haplotype is associated with lower activity of the disease, and ATA haplotype with persistent eruption [114]. As ATA is related to low IL-10 secretion [116], differences in IL-10 secretion level might contribute to the differences in the clinical course of psoriasis.

Associations between IL-19, IL-20 and IL-24 polymorphisms and psoriasis have also been assessed. Minor alleles of the IL-19 gene revealed a protective effect as regards psoriasis, but combined haplotype analysis of the IL-19 and IL-20 genes demonstrated that the protective effect of the IL-19 gene is secondary to the susceptibility effect of the IL-20 gene [117, 118]. While the IL-19/IL-20 haplotype CACCGGAA is a susceptibility factor for psoriasis [118], a significant protective effect of the combined haplotype CAAAC of the IL-20 and IL-24 genes against plaque-type psoriasis has been established [119]. Nevertheless, family-based studies are required to confirm the implication of IL-19, IL-20 and IL-24 genes in the predisposition for psoriasis. Furthermore, studies concerning the effects of these haplotypes on the expression levels of IL-19, IL-20 and IL-24 are needed.

These observations have expanded the pro-inflammatory cytokine field surrounding lesional psoriatic skin. Obviously, the expression of a number of cytokines of the IL-10 family is enhanced in psoriasis. Up-regulated expression of the corresponding receptors on psoriatic keratinocytes indicates that these cytokines may play a central role in the epidermal inflammation. *In vivo* studies showed that transgenic mice overexpressing IL-20 have a thickened epider-

mis, hyperkeratosis and a compact stratum corneum, which resembles psoriasis [4]. *In vitro* data demonstrated that IL-22 is able to induce a "psoriasis-like" gene expression profile and phenotype [17]. Based on genomic screening approaches, we have highlighted the predominance of biological activities of keratinocyte IL-22 and IL-24 over IL-19, IL-20, and IL-26. However, action on other skin cells should not be ignored. Likewise, these results did not take into account the relative expression levels of IL-10-related cytokines, their receptors, or their distribution through psoriatic skin. Furthermore, the expression of cytokine-binding factors such as IL-22BP which are able to antagonize cytokine activity, has to be considered.

Currently available treatments, such as topical therapy (corticosteroids, vitamin D analogues), phototherapy or systemic therapy (cyclosporine, methotrexate) [120] are now joined by new drugs focusing on T cell activation and Th1/Th2 balance. Indeed, the interaction between T cells and antigen-presenting cells can be inhibited using anti-CD4 monoclonal antibodies or fusion proteins such as LFA-3/CD58-Ig (alefacept) and CTLA-4/CD152-Ig [121-124]. The neutralization of Th1 cytokine activities, as for TNF-α [125, 126] or immune deviation with Th2 cytokines like IL-4, IL-10 and IL-11 [109, 113, 127, 128] are also promising strategies of treatment.

Taken together, these data suggest that the cytokines of the IL-10 family could play a central role in the induction and maintenance of psoriasis, and open the way to new therapeutic strategies focusing on more specific targets, *i.e.* keratinocytes, rather than a systemic inhibition of cytokine production by T lymphocytes (*figure 3*). The blockade of these IL-10-related cytokines or their receptors, as well as others pro-inflammatory cytokines associated with psoriasis, could be a new approach for psoriasis treatment.

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