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Induction of Keratinocyte Migration via Transactivation of the Epidermal Growth Factor Receptor by the Antimicrobial Peptide LL-37

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The closure of skin wounds is essential for resistance against microbial pathogens, and keratinocyte migration is an important step in skin wound healing. Cathelicidin hCAP18/LL-37 is an innate antimicrobial peptide that is expressed in the skin and acts to eliminate microbial pathogens. Because hCAP18/LL-37 is up-regulated at skin wound sites, we hypothesized that LL-37 induces keratinocyte migration. In this study, we found that 1 μg/ml LL-37 induced the maximum level of keratinocyte migration in the Boyden chamber assay. In addition, LL-37 phosphorylated the epidermal growth factor receptor (EGFR) after 10 min, which suggests that LL-37-induced keratinocyte migration occurs via EGFR transactivation. To test this assumption, we used inhibitors that block the sequential steps of EGFR transactivation, such as OSU8-1, CRM197, anti-EGFR no. 225 Ab, and AG1478. All of these inhibitors completely blocked LL-37-induced keratinocyte migration, which indicates that migration occurs via HB-EGF-mediated EGFR transactivation. Furthermore, CRM197, anti-EGFR no. 225, and AG1478 blocked the LL-37-induced phosphorylation of STAT3, and transfection with a dominant-negative mutant of STAT3 abolished LL-37-induced keratinocyte migration, indicating the involvement of the STAT3 pathway downstream of EGFR transactivation. Finally, we tested whether the suppressor of cytokine signaling (SOCS)/cytokine-inducible Src homology 2-containing protein (CIS) family of negative regulators of STAT3 regulates LL-37-induced keratinocyte migration. Transfection with SOCS1/Jak2 binding protein or SOCS3/CIS3 almost completely abolished LL-37-induced keratinocyte migration. In conclusion, LL-37 induces keratinocyte migration via heparin-binding-EGF-mediated transactivation of EGFR, and SOCS1/Jak 2 binding and SOCS3/CIS3 negatively regulate this migration. The results of this study suggest that LL-37 closes skin wounds by the induction of keratinocyte migration. The Journal of Immunology, 2005, 175: 4662–4668.

Antimicrobial peptides are short amino acid sequences that can kill a variety of microbial pathogens. The major human antimicrobial peptides are the defensins and cathelicidin (1–4). Defensins are cysteine-rich cationic peptides and are further classified as α- or β-defensins based on structure. The α-defensins 1–4 (HNP1–4) are produced by neutrophils (5, 6), and the α-defensins 5 and 6 are found in Paneth cells of the gastrointestinal tract (7, 8). The β-defensins 1–4 (hBD 1–4) are produced by epithelial tissues (9–12). hCAP18/LL-37 is the only human antimicrobial peptide that has been identified as a member of the cathelicidin family; it is produced in many tissues and cell types (4) and is processed to LL-37 in neutrophils (13). In the skin, epidermal keratinocytes produce hBD1–4 and hCAP18/LL-37 (4, 9–12). Murakami (14) analyzed sweat samples and identified three additional forms of cathelicidin peptide which deliver innate effector molecules in the absence of inflammation. Mast cells in the dermis were also found to produce hCAP18/LL-37 (15).

The epidermis plays an essential role in resistance against microbial-borne disease, as it is constantly exposed to a variety of microbial pathogens. The hBDs and hCAP18/LL-37 play major roles in this innate immune system (16). In addition, the epidermis functions as a physical barrier to microbial pathogens. However, once this physical barrier is disrupted by wounding, microbial pathogens can invade the underlying tissue. Therefore, the efficient closure of skin wounds is vital to the maintenance of homeostasis. In contrast, wounded skin expresses antimicrobial peptides, such as hCAP18/LL-37 and defensins (17–19). Although antimicrobial peptides were originally identified as molecules that kill microbial pathogens, there is strong evidence that these peptides have functions in antimicrobial immunity other than direct antimicrobial activity.
Recently, it was revealed that these antimicrobial peptides are multifunctional proteins (20). Although hBDs are chemotactic for dendritic cells, LL-37 is chemotactic for neutrophils, monocytes, and T cells, but not for dendritic cells (3, 21, 22). LL-37 modulates dendritic cell differentiation and promotes Th1 responses (23). In the case of endothelial cells, LL-37 induces angiogenesis that is mediated by the formyl peptide receptor-like 1 receptor (24). In wounded skin, hCAP18/LL-37 is up-regulated, whereas the hCAP18/LL-37 levels in chronic ulcers are low (19). Furthermore, anti-LL-37 Ab inhibits re-epithelialization of skin wounds (19). These findings suggest that, apart from having antimicrobial activity, LL-37 plays an important role in wound healing.

The migration of epidermal keratinocytes is an important step in skin wound healing. Growth factors and the epidermal growth factor (EGF) receptor (EGFR) are involved in keratinocyte migration and proliferation (25, 26). Extracellular stimuli from the EGF and non-EGF families can activate the EGFR. These diverse stimuli include numerous agonists for heptahelical G-protein-coupled receptors, cytokines, and integrins (27, 28). The activation of the EGFR by non-EGFR ligands is called transactivation (27) and is mediated, at least in part, by heparin-binding EGF (HB-EGF), which is cleaved from its membrane-anchored form (pro-HB-EGF) by a specific metalloproteinase (29, 30). Recently, the transactivation of EGFR by LL-37 was reported for airway epithelial cells (31), which suggests that LL-37 induces keratinocyte migration via EGFR transactivation during skin wound healing.

The intracellular signaling molecule, STAT3, is involved in keratinocyte migration (32). The STAT family consists of STAT1, 2, 3, 4, 5a, 5b, and 6. STATs and adaptor molecules are sequentially activated upon the binding of a cytokine to its receptor. After phosphorylation, STAT forms a homodimer or heterodimer, translocates into the nucleus, and initiates the transcription of target genes (33). These STAT signaling pathways are negatively regulated by the suppressor of a cytokine signaling (SOCS)/cytokine-inducible Src homology 2-containing protein (CIS) family, thereby avoiding oversignaling (34). In human keratinocytes, SOCS1/JAK2-binding (JAB) (AxCAJAB), and SOCS3/CIS3 (AxCACIS3) negatively regulates hepatocyte growth factor-induced migration (35). Therefore, the STAT3-SOCS/CIS family may also be involved in LL-37-induced keratinocyte migration.

In this study, we demonstrate that LL-37 induces keratinocyte migration, and we examine the molecular mechanisms underlying EGFR transactivation.

Materials and Methods

Synthesis of LL-37

LL-37 was synthesized using a peptide synthesizer (Shimazu), as described previously (36). The peptide was purified using reverse-phase HPLC with an octadecyl-4PW column (Tosoh) and a linear gradient of aqueous 0.05% trifluoroacetic acid to 100% acetonitrile that contained 0.05% trifluoroacetic acid, and the sample was then lyophilized to remove the organic solvent. To confirm peptide purity and quality, mass spectrometry using the MALDI/TOF-mass spectrometry method was performed with Voyager (PerSeptive Biosystems). The peptides were assayed for LPS contamination by the Limulus test (Seikagaku).

Reagents and Abs

The following Abs were used: STAT3 (clone 84; BD Transduction Laboratories), phospho-STAT3 (no. 9131; Cell Signaling Technology), EGFR (clone 13; BD Transduction Laboratories), and phospho-EGFR (clone 9H2; Upstate Biotechnology) and EGFR neutralizing Ab (clone 13; BD Transduction Laboratories), phospho-STAT3 (no. 9131; Cell Signaling Technology), EGFR

Migration assay

Keratinocyte migration was assayed quantitatively with a Boyden chamber, as described previously (40). Designated amounts of LL-37 were added to the bottom wells of a 48-well Boyden chamber (Neuro Probe), and an 8-μm pore-size polyvinylpyrrolidone-free polycarbonate membrane (Neuro Probe) was placed on the wells. The membrane was precoated with type I collagen (10 μg/ml in PBS; Nitta Gelatin) at room temperature for 1 h and then washed extensively with PBS. Subconfluent keratinocytes were harvested with trypsin-EDTA (0.05% trypsin and 0.5 mM EDTA) and resuspended in culture medium without BHE at 1 × 10^5 cells/ml. A 50-μl aliquot of the keratinocyte suspension (5,000 cells/well) was added to the upper wells, and the chamber was incubated overnight at 37°C in a humidified atmosphere of air with 5% CO_2_. The cells that adhered to the upper surface of the filter membrane were removed by scraping with a rubber blade, and the cells that moved through the filter and stayed on the lower surface of the membrane were considered to be migrated cells. The membrane was fixed with 10% buffered formalin overnight and then stained overnight with Gill’s hematoxylin. The membrane was then mounted between two glass slides with 90% glycerol, and the number of migrated cells was determined by counting under a microscope.

The role of EGFR transactivation in LL-37-induced keratinocyte migration was analyzed by the inhibition of EGFR transactivation with OSU-1-37 (anti-EGFR neutralizing Ab no. 225, CRM197 (37), and AG1478, OSU-1 (1 μM), anti-EGFR no. 225 (10 μg/ml), CRM197 (1 μg/ml), and AG1478 (30 nM) were added to the lower chamber together with 1 μg/ml LL-37, and LL-37-induced keratinocyte migration was analyzed as described previously.

Western blotting

Subconfluent keratinocytes were starved for 2 h in BHE-free medium and then stimulated with LL-37 as indicated. The cells were harvested on ice in lysis buffer that contained 5 mM EDTA, 100 mM sodium orthovandate, 100 mM sodium pyrophosphate, 1 mM sodium fluoride, 5 μM 3,4-dichloroisocoumarin, 1 μg/ml aprotinin, and 1% Triton X-100 in PBS. A 20-μg sample of protein was separated on 10% SDS-PAGE and then transferred to a polyvinylidene difluoride membrane. The membranes were blocked overnight at 4°C with 5% skimmed milk in PBS. The blocked membranes were incubated for 6 h with the first Ab as indicated. After three washes with PBS that contained 0.05% Tween 20, the membranes were treated with ABC reagents (Vector Laboratories) for 1 h. The membranes were then incubated with ECL detection reagents (Amersham Pharmacia Biotech) for 1 min at room temperature, and exposed to photographic film (Kodak).

Adenovirus vectors (Axs)

STAT3 has a phosphorylation site at tyrosine 705. In dominant-negative mutants of STAT3 (STAT3F), the phosphorylatable tyrosine residues are substituted with phenylalanine. Axs that encode STAT3F (AxCasTat3F), SOCS1/Jak2-binding (JAB) (AxCAJAB), and SOCS3/CIS3 (AxCACIS3) were generated as described previously (41), using the cosmids cassettes and Ad DNA-terminal protein complex method (42). An Axs that encodes LacZ (Ax LacZ) was a gift from Dr. I. Saito (University of Tokyo, Tokyo, Japan). Virus stocks were prepared using a standard procedure (42). Concentrated, purified virus stocks were prepared using a CsCl gradient, and the virus titer was checked using a plaque formation assay. We infected normal human keratinocytes with Axs at a multiplicity of infection (moi) of 5.

Statistical analyses

Data were collected from at least three independent experiments. Quantitative data are expressed as the mean ± SE. Statistical significance was determined by the paired Student t test. Differences were considered to be statistically significant for p < 0.05. The levels of statistical significance are indicated in the figures as follows: * p < 0.05; ** p < 0.01.
Results

LL-37 induces keratinocyte migration

Initially, we investigated whether LL-37 induced keratinocyte migration. After the addition of 1 µg/ml LL-37 to cultured normal human keratinocytes, cell migration was observed by phase contrast microscopy. LL-37 induced keratinocyte migration at 12 h compared with the control (Fig. 1A). Next, we quantitatively analyzed LL-37-induced migration using the Boyden chamber assay (Fig. 1B). Various amounts of LL-37 and cultured keratinocytes were added to the lower and upper chambers, respectively. After incubation overnight, the migrated keratinocytes were counted. LL-37 induced a 3-fold increase in keratinocyte migration compared with the control treatment. The optimum concentration of LL-37 to induce migration was 1 µg/ml.

LL-37 phosphorylates EGFR

Because EGFR is involved in keratinocyte migration, we investigated whether EGFR transactivation is involved in LL-37-induced keratinocyte migration by analyzing the phosphorylation of EGFR by LL-37 (Fig. 2). LL-37 phosphorylated EGFR at 10 min, and the phosphorylation persisted for 15 min. The amount of EGFR protein did not change during this time period.

LL-37-induced keratinocyte migration occurs via HB-EGF-mediated EGFR transactivation

The activation of EGFR suggests that LL-37-induced keratinocyte migration is via EGFR transactivation. To confirm this suggestion, we used several inhibitors that block the sequential steps of EGFR transactivation (Figs. 3 and 4B). In EGFR transactivation, extracellular stimuli activate a metalloproteinase on the cell membrane, which cleaves the extracellular domain of the EGF family. The cleaved EGF then binds and phosphorylates EGFR, which transduces the signals into the intracellular signaling pathways. OSU8-1 is a metalloproteinase inhibitor that blocks the shedding of EGF family members (37). CRM197 is a nontoxic mutant of diphtheria toxin that binds to the extracellular domain of the membrane-anchored form of HB-EGF and inhibits the soluble form of HB-EGF, whereas it does not bind to other EGF family members, such as anti-EGFR no. 225 and AG1478.
EGF, TGF-α, amphiregulin, and betacellulin (37). The anti-EGFR no. 225 Ab blocks the binding of EGF family members to the EGFR. AG1478 is an inhibitor of EGFR tyrosine kinase, which blocks the activation of EGFR.

Using these inhibitors, we investigated whether the inhibition of EGFR transactivation blocks LL-37-induced keratinocyte migration. After the addition of OSU8-1, CRM197, anti-EGFR no. 225, and AG1478 to the lower chamber with LL-37, keratinocyte migration was analyzed quantitatively using the Boyden chamber, as shown in Fig. 1. All of the inhibitors, including OSU8-1, CRM197, anti-EGFR no. 225, and AG1478, completely blocked LL-37-induced keratinocyte migration (Fig. 3). As LL-37 phosphorylates EGFR, and because LL-37-induced migration was completely blocked by OSU8-1, CRM197, anti-EGFR no. 225, and AG1478, we conclude that LL-37-induced keratinocyte migration is via HB-EGF-mediated EGFR transactivation.

**LL-37 phosphorylates STAT3 via HB-EGF-mediated EGFR transactivation**

A previous study has demonstrated that the STAT3 signaling pathway is involved in keratinocyte migration (32). Therefore, we studied the involvement of STAT3 in LL-37-induced keratinocyte migration. LL-37 maximally phosphorylated STAT3 at 15 min as determined by densitometric analysis, and the level of phosphorylation decreased at 25 min (Fig. 4). The amount of STAT3 protein did not change during this time. We also investigated whether LL-37-induced STAT3 phosphorylation occurred via HB-EGF-mediated EGFR transactivation. Keratinocytes were pretreated with OSU8-1, CRM197, anti-EGFR no. 225, and AG1478 for 1 h and were then stimulated with LL-37 for 15 min, followed by Western blot analysis. All of these inhibitors blocked LL-37-induced STAT3 phosphorylation, which again indicates that LL-37-induced STAT3 phosphorylation is via HB-EGF-mediated EGFR transactivation.

**SOCS1/JAB and SOCS3/CIS3 inhibit LL-37-induced keratinocyte migration**

Because STAT3 is involved in LL-37-induced keratinocyte migration (as shown in Figs. 4 and 5), we analyzed the mechanism of regulation of STAT3 by SOCS1/JAB and SOCS3/CIS3. After the transfection of keratinocytes with AxCAJAB or AxCACIS3, LL-37-induced keratinocyte migration was analyzed quantitatively using the Boyden chamber assay (Fig. 6). The expression of either SOCS1/JAB or SOCS3/CIS3 almost completely blocked LL-37-induced keratinocyte migration. LL-37 induced neither SOCS1/JAB nor SOCS3/CIS3 (data not shown).

**Discussion**

The molecular mechanisms underlying LL-37-induced keratinocyte migration are summarized in Fig. 7. LL-37 activates the metalloproteinase, which cleaves the extracellular domain of HB-EGF. The soluble form of HB-EGF then binds to and phosphorylates EGFR. This, in turn, transduces the signals into the intracellular signaling pathways. STAT3 mediates this signaling pathway, leading to keratinocyte migration. SOCS1/JAB or SOCS3/CIS3 negatively regulates this STAT3 pathway and migration.

In a previous study, Tjabringa et al. (31) have shown that LL-37 activates airway epithelial cells, as demonstrated by its ability to activate ERK1/2 and to increase the release of IL-8. This activation

**STAT3 is essential for LL-37-induced keratinocyte migration**

We investigated whether STAT3 is essential for LL-37-induced keratinocyte migration. We constructed dominant-negative mutants of STAT3 (STAT3F) as well as Ax-carrying STAT3F (AxCAStat3F), as described previously (41). AxCAStat3F and the control vector AxLacZ were transfected into normal human keratinocytes at a moi of 10. After 24 h, the keratinocytes were harvested and transferred to the upper well of the Boyden chamber. Then, 1 µg/ml LL-37 was added to the lower chamber, and keratinocyte migration was analyzed as described in Fig. 1. The numbers of migrated cells are shown as percentages of the control migration. Each point shows the mean ± SD of quadruplicate measurements. *p < 0.05.
requires the tyrosine kinase activity of the EGFR and involves the action of metalloproteinases and EGFR ligands, which indicates that the transactivation of EGFR is involved in this activation. The mechanism of this activation is quite similar to that of keratinocytes (Fig. 7). However, among the several EGFR ligands, no specific EGFR ligand for the transactivation of EGFR has been identified in airway epithelial cells. In keratinocytes, we found that HB-EGF is a mediator for LL-37-induced EGFR transactivation. The mechanism through which LL-37 activates metalloproteinase is still unclear. Several candidate molecules for the LL-37 receptor have been suggested, including the G protein-coupled formyl peptide receptor-like 1 (FPRL-1) (22, 24) and P2X7 (43). However, in airway epithelial cells, the activation was not inhibited by pertussis toxin or FPRL-1-antagonistic peptide, which indicates that FPRL-1 is not involved in transactivation of EGFR (31). Similarly, in keratinocytes, pertussis toxin did not inhibit LL-37-induced EGFR phosphorylation (data not shown), which suggests that FPRL-1 is not involved in LL-37-induced EGFR transactivation (Fig. 7). However, among the several EGFR ligands, no specific EGFR ligand for the transactivation of EGFR has been identified in airway epithelial cells. In keratinocytes, we found that HB-EGF is a mediator for LL-37-induced EGFR transactivation. The mechanism through which LL-37 activates metalloproteinase is still unclear. Several candidate molecules for the LL-37 receptor have been suggested, including the G protein-coupled formyl peptide receptor-like 1 (FPRL-1) (22, 24) and P2X7 (43). However, in airway epithelial cells, the activation was not inhibited by pertussis toxin or FPRL-1-antagonistic peptide, which indicates that FPRL-1 is not involved in transactivation of EGFR (31). Similarly, in keratinocytes, pertussis toxin did not inhibit LL-37-induced EGFR phosphorylation (data not shown), which suggests that FPRL-1 is not involved in LL-37-induced EGFR transactivation of keratinocytes. More recently, it has been suggested that LL-37 is able to cross the keratinocyte cell membrane and enter the cell (44). In this model, specific receptors are not required, and LL-37 may interact directly with the keratinocyte plasma membrane to cause conformational changes that activate indirectly a surface receptor that is linked to intracellular signaling molecules. If this is the case, it is possible that other highly cationic antimicrobial peptides, such as hBD1–3, also activate EGFR in keratinocytes. We tested this possibility and found that hBD1–3 phosphorylated EGFR in keratinocytes which suggests that the activation of keratinocytes is not unique to LL-37 among the antimicrobial peptides (our unpublished data).

The innate immune system is the first line of defense against microbial pathogens. Keratinocytes form a multilayered epidermis that separates the inner body from the outer environment and protects against a variety of microbial pathogens. Because the epidermis is the outermost layer of the body, epidermal keratinocytes are thought to be important components of innate immunity. Once the epidermis is disrupted by wounding, microbial pathogens can easily invade the body. Therefore, wound closure is an important issue for keratinocytes as participants in innate immunity. In this study, we have clearly demonstrated that LL-37 induces keratinocyte migration via EGFR transactivation. In the epidermis, bacterial contact, inflammation, and wounding are reported to stimulate keratinocytes to produce hCAP18/LL-37 (18, 36, 45). In addition to keratinocytes, granulocytes and skin mast cells produce hCAP18/LL-37 (4, 15). As hCAP18/LL-37 is up-regulated at the skin wound site (18), the present report strongly suggests that LL-37 induces keratinocyte migration to close the skin wound. In addition to its effects on keratinocytes, LL-37 can act on endothelial (24) and inflammatory cells, including neutrophils, monocytes, and T cells (22). Therefore, LL-37 may regulate skin wound healing through mechanisms that act directly on the cells within the wound environment rather than acting solely against microbial pathogens. Thus, hCAP18/LL-37 is a multifunctional mediator of innate immunity because it links host defenses and wound healing.

In the present study, the optimal concentration of LL-37 that induced keratinocyte migration was 1 μg/ml. The concentration of hCAP18/LL-37 at surgical wound sites has been reported to be ~2 μg/mg protein (19). Assuming that the protein concentration is similar to that in the serum (~70 mg/ml), the estimated concentration of hCAP18/LL-37 is 0.03 μg/ml. According to the data shown in Fig. 1, this concentration is insufficient to induce keratinocyte migration. However, immunohistochemical analysis has revealed that hCAP18/LL-37 is up-regulated, especially at the wound edge (19), which suggests that the local concentration of
LL-37 at the wound edge, where keratinocytes are migrating, may be high enough to induce migration.

Although we have shown that LL-37 induces keratinocyte migration, it has been reported that human serum inhibits the anti-microbial activity of LL-37 (46), which raises the possibility that serum also inhibits LL-37-induced keratinocyte migration during wound healing in vivo. In an ex vivo wound healing model, re-epithelialization occurred in two steps without inflammation, i.e., simple migration and subsequent proliferation of keratinocytes to form a provisional neoidermis (19). Our data indicate that endogenous LL-37 mediates this keratinocyte migration. This ex vivo wound healing model requires medium that contains at least 10% FBS for re-epithelialization (47, 48). Furthermore, this re-epithelialization is inhibited by anti-LL-37 Ab (19), which indicates that endogenous LL-37 is a mediator of re-epithelialization even in the presence of serum. In addition to the ex vivo wound healing model, LL-37-induced migration of leukocytes is independent of the presence of serum (22). Therefore, LL-37-induced keratinocyte migration may not be hindered by the presence of serum or wound fluid in vivo.

Growth factors, such as insulin-like growth factor-I and TGF-α, have been shown to induce the expression of hCAP18/LL-37 and hBD3 in human keratinocytes (49). In addition to these growth factors, EGF family members, including HB-EGF, are known to induce hCAP18/LL-37 in keratinocytes (our unpublished data). The EGF family is thought to be involved in the re-epithelialization of skin wounds (50). Among the EGF family, HB-EGF is a major growth factor component of wound fluid (51). Wound stimuli induce the shedding of HB-EGF from keratinocytes (37). In psoriasis, hCAP18/LL-37 is up-regulated in the lesional epidermis (52). Because EGF family expression is enhanced in the lesional skin of psoriasis patients (53, 54), these elevated levels of hCAP18/LL-37 may be due to increased levels of EGF family proteins.

We also analyzed the regulation of STAT3 activation during LL-37-induced keratinocyte migration. The SOCS/CIS family negatively regulates the STAT pathways (34, 55, 56). However, the inhibitory functions of the SOCS/CIS family differ according to the cell type and cellular conditions. In this study, we showed that SOCS1/JAB or SOCS3/CIS3 block LL-37-induced keratinocyte migration, which suggests that migration is inhibited under conditions of high-level SOCS1/JAB or SOCS3/CIS3. Cytokines, such as IFN-γ, IL-4, and IL-6, have been implicated in a variety of physiological and pathological conditions of the skin. IFN-γ enhances SOCS1/JAB and SOCS3/CIS3 expression (41) in normal human keratinocytes. In addition, IL-4 and IL-6 enhance the expression of SOCS1/JAB and SOCS3/CIS3, respectively, in normal human keratinocytes (41). Therefore, the possibility exists that IFN-γ, IL-4, and IL-6 affect wound healing in various inflammatory skin conditions by regulating keratinocyte migration via the induction of SOCS1/JAB or SOCS3/CIS3, which would lead to sustained wound healing in chronic ulcers. However, SOCS1/JAB and SOCS3/CIS3 were not induced by LL-37, which indicates that SOCS1/JAB and SOCS3/CIS3 do not act as self-liming factors in LL-37-induced keratinocyte migration.

In conclusion, LL-37 induces keratinocyte migration via HB-EGF-mediated EGFRT transactivation and STAT3 phosphorylation.

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LL37 INDUCES KERATINOCYTE MIGRATION VIA EGFR TRANSACTIVATION


