Koebnerisin (S100A15): A novel player in the pathogenesis of rosacea

To the Editor: Rosacea is one of the most common chronic inflammatory skin diseases that mainly affects the white adult population. The pathophysiology of rosacea is still not completely elucidated. Growing evidence indicates that the aberrant innate immune response might play an essential role in this disease.[1]

S100 proteins are a family of small (9-13 kDa), calcium-binding molecules involved in the regulation of cell signaling, metabolism, and proliferation. A member of the S100 protein family, koebnerisin (S100A15), is an innate, antimicrobial peptide with diverse proinflammatory functions encoded by a gene located within the epidermal differentiation complex on chromosome 1q21. The S100A15 gene is transcribed into 2 alternate mRNA splice variants, the short (S100A15-S) and long (S100A15-L) isoforms, that share the same coding region but are differentially regulated.[2] Koebnerisin has been shown to act as an alarmin or has a danger-associated molecular pattern (DAMP). In response to some endogenous or exogenous stimuli, koebnerisin enhances immune-mediated inflammatory processes in the skin.[2-4] Koebnerisin was first found to be up-regulated in psoriatic skin lesions; however, it also appears to play an important role in other chronic inflammatory skin diseases, such as acne vulgaris.[2,5] In inflamed skin, koebnerisin is expressed by various cells, such as keratinocytes, fibroblast, endothelial cells, and dendritic cells.[2] The role of koebnerisin in rosacea has not been investigated. The objective of the present study was to investigate the expression and function of koebnerisin in rosacea.

The study group consisted of patients with moderate and severe rosacea (n = 6). Skin biopsies were taken from inflammatory, erythematopapular lesions located on the face. All patients were white, had skin of phototype I-III, and were 47-66 (mean ± standard deviation 56.83 ± 7.03) years of age. The control group was matched by race, sex, and age and consisted of healthy volunteers who underwent facial plastic surgery procedures (n = 6). The expression of koebnerisin in skin lesions of patients with rosacea and controls was assessed by quantitative reverse transcription PCR and immunofluorescent analysis. The regulation and function of koebnerisin in rosacea-relevant human skin cell cultures, keratinocytes, and

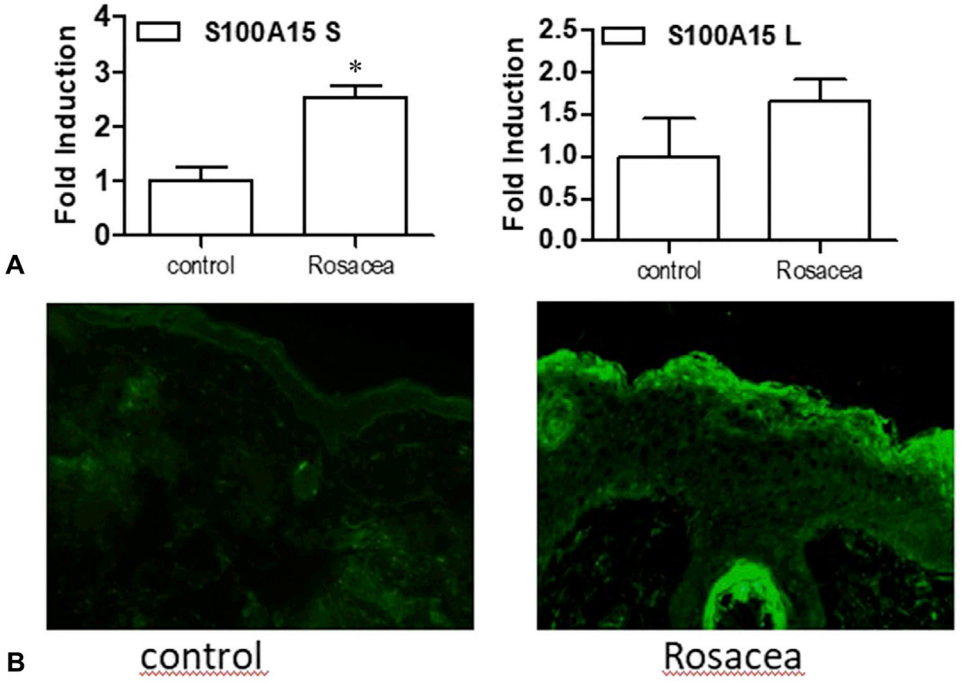

Fig 1. Koebnerisin is overexpressed in lesional skin form patients with moderate and severe rosacea. **A**, Quantitative reverse transcription PCR. Increased expression of koebnerisin isoform (S100A15S) in human rosacea lesional skin compared with healthy human skin. Data represent mean ± standard error of the mean. **B**, Immunofluorescent staining. Increased expression of koebnerisin in human rosacea lesional skin compared with healthy human skin. *$P = .0087$

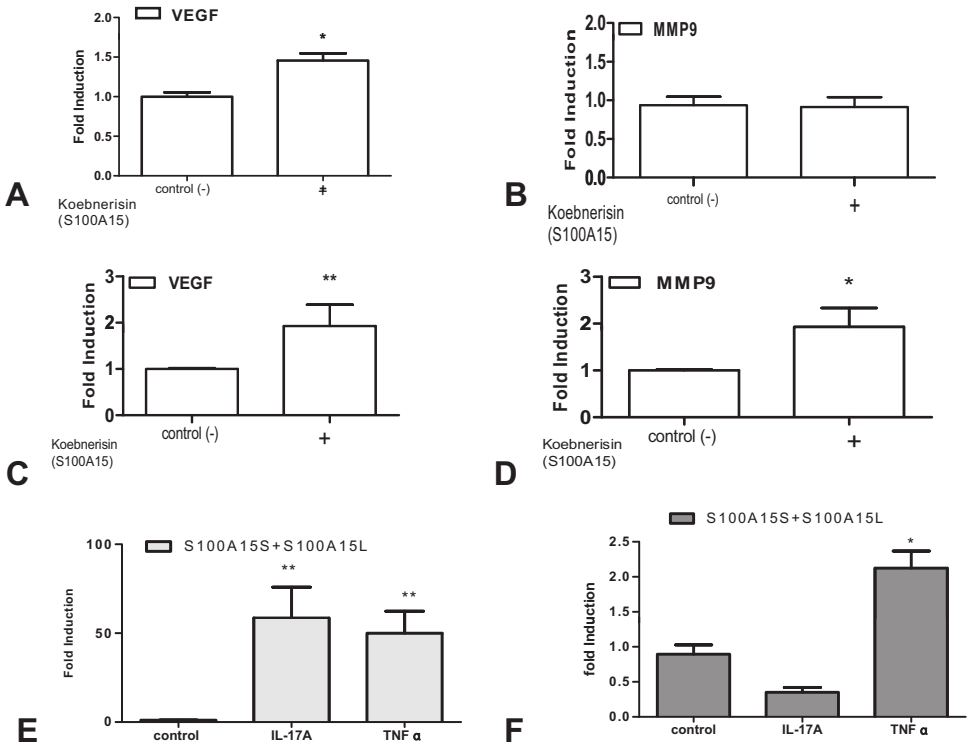

Fig 2. Quantitative reverse transcription PCR of mRNA in healthy human skin and lesional skin from patients with moderate and severe rosacea. **A** and **B**, Koebnerisin (S100A15) enhances the expression of VEGF and does not influence the expression of MMP-9 in human keratinocytes. **C** and **D**, Koebnerisin enhances the expression of VEGF and MMP-9 in human fibroblasts. **E**, TNF-α and IL-17A enhances the expression of koebnerisin in human keratinocytes **F**, TNF-α enhances the expression of koebnerisin in human fibroblasts. Data represent mean ± standard error of mean. *$P = .05$. *IL-17A*, Interleukin 17A; *MMP-9*, matrix metalloproteinase-9; *TNF-α*, tumor necrosis factor α; *VEGF*, vascular endothelial growth factor.

fibroblasts were assessed by quantitative reverse transcription PCR.

In the present study, we found that koebnerisin was upregulated in rosacea lesional skin compared with healthy skin (Fig 1). Koebnerisin was overexpressed in the epidermis by suprabasal and basal keratinocytes as well as in the dermis. The upregulation of koebnerisin in the epidermis suggests its potential role in the regulation of keratinocytes proliferation and function. Moreover, by being overexpressed in rosacea skin lesions, koebnerisin might exert a proinflammatory effect. A previously conducted study showed that koebnerisin acts as a chemoattractant for monocytes and neutrophils, which play a significant role in the pathogenesis of rosacea.[3] Furthermore, it has been demonstrated that koebnerisin has the ability to prime keratinocytes and leukocytes for enhanced production of proinflammatory cytokines, eg, tumor necrosis factor α (TNF-α), interleukin (IL) 6, IL-8, and IL-1β.[4,6] Recent studies have indicated a significant role for TNF-α and IL-1β in rosacea.[1] We also demonstrated that TNF-α enhanced the expression of koebnerisin in keratinocytes and fibroblasts (Fig 2, *A* and *B*), which might create a vicious circular cycle of inflammation. In the present study, we also showed that koebnerisin might play an additional proangiogenic role stimulating keratinocytes and fibroblasts to enhance the production of the potent proangiogenic mediator vascular endothelial growth factor, and we further demonstrated that koebnerisin primed fibroblasts for increased expression of matrix metalloproteinase 9 (Fig 2, *C-F*). Matrix metalloproteinase 9 has a destructive effect on

dermal components and, thus, stimulates the innate immune response and inflammatory processes.[1]

In conclusion, koebnerisin (S100A15) might emerge as a novel player in the pathogenesis of rosacea. Balancing the activities of certain antimicrobial proteins might be a goal for future therapeutic interventions in rosacea.

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Pigmentation of basal cell carcinoma is inversely associated with tumor aggressiveness in Asian patients

To the Editor: Previous studies have suggested pigmented basal cell carcinomas (BCCs) predominate in Asians and that increased pigmentation might be associated with better prognosis.[1-4] Owing to easily recognizable boundaries, complete excision with clear margins might be sufficient to treat well-defined, pigmented BCCs.[3,4] However, the association between pigmentation and better prognosis is limited by the absence of a definite cut-off value for pigmentation and the lack of consideration of conventional prognostic factors. Therefore, we sought to correlate subclinical infiltration of BCCs with the quantitative assessment of pigmentation, while controlling for known prognostic factors.

We retrospectively investigated primary BCCs treated with Mohs micrographic surgery (MMS) during 2004-2017. The pigmentary area of tumor was estimated by using an image processing software (ImageJ; National Institutes of Health, Bethesda, MD). After converting the clinical photographs obtained before the biopsy or surgery to grayscale mode, the pigmented extent of BCCs was calculated as the percentage of the sum of black-colored pixels over the total number of pixels in the tumor surface.

Among the 225 BCCs, 179 (79.6%) were located on the face, with many located on the nose (Table I). The tumor size was significantly associated with the number of MMS stages required for clearance ($P = .01$). Ulceration (97 tumors, 43.1%) was not associated with MMS stage ($P = .734$). There was a significant inverse association between the percentage of pigmented area and the MMS stage ($P < .001$).

According to the surface pigmented area of tumor, nodular BCCs were presented with a large pigmented area ($P = .007$), whereas morpheaform and infiltrative BCCs tended to be less pigmented ($P = .001$ and $P = .002$).

In multiple logistic regression analyses (Table II), the pigmented area of the tumor surface ($P = .035$, 95% confidence interval [CI] −0.045 to −0.01), tumor size ($P = .025$, 95% CI 0.053−0.808), and aggressive histologic subtype ($P < .001$, 95% CI 1.160−2.469) were independently associated with the number of MMS stages.

Our study demonstrated that more heavily pigmented BCCs required fewer MMS stages to achieve clearance. Furthermore, aggressive histologic BCC subtypes presented with a lesser extent of pigmentation compared with nonaggressive subtypes. There is a possible explanation for less aggressive characteristics