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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REFERENCES

1. Gallo RL, Granstein RD, Kang S, et al. Standard classification and pathophysiology of rosacea: the 2017 update by the National Rosacea Society Expert Committee. *J Am Acad Dermatol*. 2018;78:148-155.
2. Wolf R, Ruzicka T, Yuspa SH. Novel S100A7 (Psoriasin)/S100A15 (koebnerisin) subfamily: highly homologous but distinct in regulation and function. *Amino Acids*. 2011;41:789-796.
3. Wolf R, Howard OM, Dong HF, et al. Chemotactic activity of S100A7 (Psoriasin) is mediated by the receptor for advanced glycation end products and potentiates inflammation with highly homologous but functionally distinct S100A15. *J Immunol*. 2008;181:1499-1506.
4. Hegyi Z, Zwicker S, Bureik D, et al. Vitamin D analog calcipotriol suppresses the Th17 cytokine-induced pro-inflammatory S100 "alarmins" Psoriasin (S100A7) and koebnerisin (S100A15) in psoriasis. *J Invest Dermatol*. 2012;132:1416-1424.
5. Borovaya A, Dombrowski Y, Zwicker S, et al. Isotretinoin therapy changes the expression of antimicrobial peptides in acne vulgaris. *Arch Dermatol Res*. 2014;306:689-700.
6. Batycka-Baran A, Hattinger E, Zwicker S, et al. Leukocyte-derived koebnerisin (S100A15) and Psoriasin (S100A7) are systemic mediators of inflammation in psoriasis. *J Dermatol Sci*. 2015;79:214-221.

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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

Table I. Demographic data, clinical characteristics, and histopathologic subtypes of BCCs according to MMS stage

Characteristic	Total	MMS stage 1	MMS stage 2	MMS stage 3	MMS stage 4	MMS stage 5	*P* value
N (%)	225 (100)	151 (67.1)	58 (25.8)	11 (4.9)	3 (1.3)	2 (0.9)	
Sex, n (%)							.994
Male	84 (38.3)	57 (25.3)	25 (11.1)	2 (0.9)	1 (0.4)	1 (0.4)	
Female	135 (61.7)	94 (41.7)	33 (14.7)	9 (4.0)	2 (0.9)	1 (0.4)	
Age at diagnosis, y, mean ± SD	68.3 ± 13.7	68.5 ± 13.9	69.9 ± 13.0	71.0 ± 10.8	46.6 ± 12.5	61.5 ± 9.2	.812
Site of lesion, n (%)							
High-risk area							
Periorbital	23 (10.2)	15 (6.7)	7 (3.1)	1 (0.4)	0	0	.935
Periauricular	15 (6.7)	10 (4.4)	4 (1.8)	0	1 (0.4)	0	.964
Nose	74 (32.8)	44 (19.6)	21 (9.3)	5 (2.2)	2 (0.9)	1 (0.4)	.106
Perioral	7 (3.1)	7 (3.1)	0	0	0	0	.785
Medium-risk area							
Scalp	20 (8.9)	14 (6.2)	5 (2.2)	1 (0.4)	0	0	.720
Forehead	17 (7.6)	12 (5.3)	3 (1.3)	2 (0.9)	0	0	.863
Cheek	52 (23.1)	32 (14.2)	17 (7.6)	2 (0.9)	0	1 (0.4)	.416
Low-risk area							
Trunk	10 (4.4)	9 (4.0)	1 (0.4)	0	0	0	.183
Extremities	7 (3.1)	7 (3.1)	0	0	0	0	.078
Size, cm, mean ± SD	1.30 ± 0.81	1.22 ± 0.80	1.48 ± 0.87	1.64 ± 0.59	1.33 ± 0.76	0.80 ± 0.28	**.011**
Ulceration, n (%)	94 (43.7)	66 (30.7)	23 (10.7)	4 (1.9)	1 (0.5)	0 (0)	.734
Pigmentation, %, mean ± SD	39.5 ± 35.4	44.7 ± 35.7	31.5 ± 32.7	15.4 ± 31.4	1.7 ± 2.9	28.0 ± 15.6	**<.001**
Nonaggressive							
Nodular	123 (54.6)	88 (58.3)	32 (55.2)	3 (27.3)	0	0	**.049**
Superficial	53 (23.5)	40 (26.5)	11 (19.0)	1 (9.1)	1 (33.3)	0	.123
Adenoid	37 (16.4)	25 (16.6)	11 (19.0)	1 (9.1)	0	0	.787
Follicular	5 (2.2)	4 (2.6)	1 (1.7)	0	0	0	.498
Aggressive							
Morpheaform	26 (11.6)	14 (9.3)	8 (13.8)	2 (18.2)	1 (33.3)	1 (50.0)	.083
Infiltrative	40 (17.8)	17 (11.3)	16 (27.6)	6 (53.5)	1 (33.3)	0	**<.001**
Micronodular	20 (8.9)	7 (4.6)	10 (17.2)	2 (18.2)	1 (33.3)	0	**.001**
Basosquamous	2 (0.9)	0	0	1 (9.1)	0	1 (50.0)	**.001**

Values considered statistically significant ($P < .05$) are bold.
BCC, Basal cell carcinoma; *MMS*, Mohs micrographic surgery; *SD*, standard deviation.

of pigmented BCCs through the effect of pigmentation on histologic subtypes. Nonaggressive BCCs might grow with well-differentiated patterns and preserve relatively more melanocytes in the tumor burden. On the contrary, higher proportions of melanin might prevent the development of advanced BCCs. Nonpigmented BCCs, without the protective effect of melanin, might be able to proceed along a more aggressive growth pattern.

Limitations of our study include its retrospective and single-center design, focus on 1 ethnicity (the Korean population), and use of the number of MMS stages to evaluate prognosis. However, our study demonstrated the inverse relationship between pigmentation and MMS stages using the novel concept of a semiquantitative approach in pigmentation. Pigmentation in BCCs should be considered a favorable histologic feature.

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Table II. Risk factors for subclinical infiltration of BCC in univariate and multiple logistic regression analyses

Factors	*P* value (95% CI)
Univariate analysis	
Age	.812
Sex	.994
Size	**.011**
High-risk location	.369
Size and high-risk location	.219
Pigmentation	**<.001**
Ulceration	.734
Aggressive histologic subtype	**<.001**
Multiple logistic regression analysis	
Age	.061 (−0.43 to 0.005)
Sex	.771 (−0.467 to 0.857)
Size	**.025 (0.053 to 0.808)**
Pigmentation	**.035 (−0.045 to −0.01)**
Aggressive histologic subtype	**<.001 (1.160 to 2.469)**

Values considered statistically significant ($P < .05$) are bold.
BCC, Basal cell carcinoma; *CI*, confidence interval; *MMS*, Mohs micrographic surgery.

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REFERENCES

1. Ro KW, Seo SH, Son SW, et al. Subclinical infiltration of basal cell carcinoma in Asian patients: assessment after Mohs micrographic surgery. *Ann Dermatol*. 2011;23:276-281.
2. Takenouchi T, Takatsuka S. Long-term prognosis after surgical excision of basal cell carcinoma: a single institutional study in Japan. *J Dermatol*. 2013;40:696-699.
3. Ito T, Inatomi Y, Nagae K, et al. Narrow-margin excision is a safe, reliable treatment for well-defined, primary pigmented basal cell carcinoma: an analysis of 288 lesions in Japan. *J Eur Acad Dermatol Venereol*. 2015;29:1828-1831.
4. Lin SH, Cheng YW, Yang YC, et al. Treatment of pigmented basal cell carcinoma with 3 mm surgical margin in Asians. *Biomed Res Int*. 2016;2016:7682917.

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Long-term sheltering mustaches reduce incidence of lower lip actinic keratosis

To the Editor: Actinic keratoses (AKs) are precursors to cutaneous squamous cell carcinomas (cSCCs). Although all AKs can progress to cSCCs, (1) lip AKs progress more often and (2) lip cSCCs are more likely to metastasize.[1-3] The rate of progression from nonlip AK to cSCC is generally reported to be less than 0.5%,[4] and the metastatic rate for nonlip cSCC is 2% to 3%.[1] In contrast, the rate of progression of lip AK to cSCC has been reported to be 14% to 17%,[2,3] and lip cSCC has a metastatic rate of approximately 11%.[1]

Flohil et al demonstrated that whereas the scalp's upward-facing surface receives increased exposure to ultraviolet light and carries an elevated risk of AK, scalp hair can protect against scalp AK.[5] Similarly, lip AKs nearly always occur on the upward-facing and more ultraviolet-exposed lower lip, not on the downward-facing and relatively protected upper lip. The lip may be especially susceptible to AK on account of its thin keratin layer, reduced melanin content, and lower sebaceous and sweat secretions.

To study the impact of mustaches on lip AK, we assessed 200 male subjects with AK on the head and face: 59 who reported having had sheltering mustaches continuously since their early 20s (test group) and 141 who did not (control group). Sheltering was generally defined as a mustache greater than 9 mm in length, but anatomic exceptions were made (eg, an underbite required a longer mustache). A total of 141 other male patients with head and/or face AKs were included as controls. Data were analyzed by using RStudio software (RStudio, Inc, Boston, MA), followed by multivariate logistic regression analysis.

Known risk factors for development of an AK include occupational and/or recreational sun exposure, blistering sunburns, history of skin cancer, immunosuppression, tobacco use, age older than 65 years, and family history of skin cancer.[5] Recursive partitioning classification tree analysis revealed that 4 of these risk factors were significant in our data set. Multivariate logistic regression analysis of those 4 risk factors showed that whereas age had a minimal impact ($P = .008$) and family history of skin cancer and sunburns roughly doubled the risk of a lip AK ($P = .019$ and .029, respectively), mustaches reduced risk the risk of a lower lip AK by a factor of 16 ($P = .0003$). Thus, among patients who already had a head AK, mustaches had the greatest and most significant impact on reducing risk of a lower lip AK (Table I and Fig 1 [available at http://www.jaad.org]).

Because all subjects already had an AK on the head, it is not entirely surprising that immunosuppression did not independently increase the incidence of lip AKs. However, because immunosuppression is of such importance in dermatology, a separate subanalysis examined the 41 immunocompromised subjects. Of the 22 without sheltering mustaches, 7 had lower lip AKs, whereas none of the 19 with mustaches had a lower lip AK $P = .02$). This supports a protective effect of mustaches in immunocompromised individuals.

The limitations of our study include the fact that all subjects came from a tertiary dermatology clinic population that was greatly enriched for risk factors