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INVESTIGATIVE REPORT

Cadherin 11 Involved in Basement Membrane Damage and Dermal Changes in Melasma

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Basement membrane (BM) disruption and dermal changes (elastosis, collagenolysis, vascular ectasia) have been reported in melasma. Although ultraviolet (UV) irradiation can induce these changes, UV is not always necessary for melasma development. Cadherin 11 (CDH11), which is upregulated in some melasma patients, has previously been shown to stimulate melanogenesis. Because CDH11 action requires cell–cell adhesion between fibroblasts and melanocytes, BM disruption *in vivo* should facilitate this. The aim of this study was to examine whether CDH11 overexpression leads to BM disruption and dermal changes, independent of UV irradiation. Immunohistochemistry/immunofluorescence, real-time PCR, Western blotting, and zymography suggested that BM disruption/dermal changes and related factors were present in the hyperpigmented skin of CDH11-upregulated melasma patients and in CDH11-overexpressing fibroblasts/keratinocytes. The opposite was seen in CDH11-knockdown cells. UV irradiation of the cultured cells did not increase CDH11 expression. Collectively, these data demonstrate that CDH11 overexpression could induce BM disruption and dermal changes in melasma, regardless of UV exposure. ***Key words: CDH11; basement membrane disruption; dermal changes; melasma; UV-independent.***

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Melasma is a pattern of skin pigmentation with increased deposition of melanin in the epidermis and dermis. No other clinical changes, other than hyperpigmentation, are seen with the naked eye. However, light microscopy often reveals disruption to the basement membrane (BM) in hyperpigmented skin, with movement of melanocytes into the dermis (1). Abundant elastotic material (2, 3) and an increased number and size of blood vessels (4) have also been reported as dermal changes in hyperpigmented skin compared with normally pigmented skin. Damaged BM could allow melanin to migrate into the dermis (1), inducing the dermal type of melasma (5). Along with genetic predisposition and the presence of female sex hormones, ultraviolet (UV) irradiation is a main cause of melasma (6), and can induce these microscopic changes (7–9). However, UV irradiation is not always necessary in melasma development. Other factors, such as H19 RNA downregulation (10) and Wnt inhibitory factor 1 downregulation (11), have also been implicated in melasma development without a contribution by UV irradiation.

H19 RNA is a non-coding RNA (10), which acts through miR-675, a microRNA of H19 (12). Expression of miR-675 is decreased in some of patients with melasma, which reduces melanogenesis through inhibition of their target expression. One of the targets of miR-675 is cadherin11 (CDH11), which is a classic member of the cadherins. The cadherin family makes up a group of Ca^{2+}-dependent transmembrane cell adhesion molecules (13). CDH11 is cloned from a mouse osteoblastic cell line (14) and its expression has been mostly in cells of mesodermal origin (15). In the skin, CDH11 is expressed mainly in dermal fibroblasts and, to a lesser extent, in keratinocytes, but not in melanocytes. CDH11 induces expression of N-cadherin in dermal fibroblasts and keratinocytes and increases melanogenesis through cell–cell homophilic adhesion between fibroblasts (or keratinocytes) and melanocytes via N-cadherin (13).

The above findings are from *in vitro* culture experiments. For an *in vivo* role of CDH11 in melanogenesis stimulation, a direct cell–cell adhesion, in particular between fibroblasts and melanocytes, is required, which should be accompanied by disruption of the BM and migration of fibroblasts to the BM. It is uncertain whether CDH11 itself is involved in BM disruption as well as the dermal changes found in melasma. This study addresses the above question, along with the role of CDH11-induced dermal changes in melasma (collagenolysis, accumulation of elastotic material, and vascular ectasia) independent of UV exposure. Results from skin specimens of melasma patients showing CDH11 upregulation and cultured fibroblasts and keratinocytes with CDH11 overexpression and CDH11 knockdown suggest that CDH11 could be involved in the changes seen in the BM and dermis in melasma, independent of UV irradiation.

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MATERIALS AND METHODS (see also Appendix S1[1])

Study using patient skin specimens

Eleven female melasma patients with CDH11 upregulation were included in the present study. Pairs of hyperpigmented and adjacent normally pigmented skin specimens located on the lateral side of the upper cheek were biopsied for histological analysis (Masson's trichrome and Verhoeff staining), immunohistochemical analysis (collagen I, matrix metalloproteinases (MMPs)-2 and -9, vascular endothelial growth factors (VEGFs)-A and -D) or real-time PCR (collagen type IVα1 and IVα2).

Study using cultured normal human skin cells

Adult skin specimens obtained from Caesarean sections and circumcisions were used to establish keratinocytes and fibroblasts in culture.

The cells with CDH11 overexpression or CDH11 knockdown were used for Western blot analysis (collagens I and IV, MMPs-1, -2, -3 and -9, tissue inhibitors of metalloproteinases (TIMPs)-1 and -2, CDH11, VEGFs-A and -D), immunohistochemical analysis (collagens I and IV, MMPs-2 and -9, VEGFs-A and -D), or zymogram (MMPs-2 and -9). The cells irradiated with narrow-band ultraviolet B (NB-UVB) were used for Western blot analysis (MMPs-1 and -2, TIMPs-1 and -2, CDH11).

Statistical analysis

Statistical analysis of the experimental data was performed using a Student's *t*-test.

RESULTS

Correlation of CDH11 expression with BM damage and dermal changes in patients with melasma

In order to identify the role of CDH11 in BM damage, skin samples from 7 female melasma patients were chosen. The patient samples showed more intense staining against the anti-CDH11 antibody in their hyperpigmented skin compared with adjacent normally pigmented skin ($p < 0.05$, Fig. 1A).

Immunofluorescence staining with an anti-type IV collagen antibody showed intermittently weaker staining intensities along the BM of the hyperpigmented skin (Fig. 1A). Reduced type IV collagen in the hyperpigmented skin was also identified by real-time PCR ($p < 0.05$, Fig. 1A). Masson's trichrome and Verhoeff staining in size-matched areas from paired hyperpigmented and normally pigmented dermis showed a decreased collagen level ($p < 0.05$, Fig. 1B), but an increased elastotic material content in the hyperpigmented dermis ($p < 0.05$, Fig. 1C). Because an increase in matrix metalloproteinase-1 (MMP-1) initiates cleavage of type I collagen (16) and increased MMP-1 and MMP-2 could be involved in elastotic material development (17), immunofluorescence staining with anti-MMP-1 and MMP-2 antibodies was performed. Stronger staining intensities of MMP-1 and MMP-2 were detected in the epidermis and dermis of the hyperpigmented skin, without an increase in MMP-2 expression in the basal layer ($p < 0.05$, Fig. 1D). Immunofluorescence intensities of VEGF-D were stronger in the hyperpigmented dermis, and those of VEGF-A were more intense in the hyperpigmented epidermis ($p < 0.05$, Fig. 1E).

Effect of CDH11 on the in vitro *expression of collagen, MMPs and TIMPs*

Since the above findings suggested an effect of CDH11 on the expression of collagens, MMPs and VEGFs, and keratinocytes and fibroblasts are the main source of type I and IV collagens, with different types of MMPs (including MMP-1, MMP-2 and MMP-9) and TIMPs (TIMP-1 and TIMP-2) expressed in skin (18, 19), we next examined the expression levels in primary cultured normal human fibroblasts and keratinocytes relative to CDH11 overexpression or knockdown.

CDH11 overexpression in fibroblasts decreased type I collagen expression, whereas CDH11 knockdown increased the expression levels ($p < 0.05$, Fig. 2A), and this matched the immunofluorescence staining with anti-type I collagen antibody (Fig. 2B). In keratinocytes, CDH11 overexpression decreased type IV collagen expression ($p < 0.05$, Fig. 2C) and immunofluorescence staining with anti-type IV collagen antibody (Fig. 2D).

With regard to MMP-1 and MMP-2, CDH11 overexpression in fibroblasts significantly increased their expression, whereas CDH11 knockdown decreased them ($p < 0.05$, Fig. 2E). Stronger immunofluorescence staining with anti-MMP-2 antibody was seen in CDH11-overexpressing fibroblasts (Fig. 2F). Conversely, expression of TIMP-1 and TIMP-2 was decreased by CDH11 overexpression and increased by CDH11 knockdown ($p < 0.05$, Fig. 2E).

In keratinocytes, the CDH11 effects on MMP-1 were similar to those seen in fibroblasts (Fig. 2G). Changes in MMP-9 expression were significant ($p < 0.05$, Fig. 2G), and stronger staining intensities of MMP-9 expression were found in CDH11-overexpressing keratinocytes (Fig. 2H). Changes in MMP-2, TIMP-1 and TIMP-2 expression were hardly noticeable in keratinocytes with CDH11 overexpression or knockdown. Zymography using culture supernatants showed that the activities of MMP-2 and MMP-9 in monolayer-cultured fibroblasts with CDH11 overexpression, and those of MMP-9 in keratinocytes with CDH11 overexpression, were higher than those without CDH11 overexpression ($p < 0.05$, Fig. 2I).

Effect of CDH11 on the expression of VEGFs

The VEGF family includes VEGF-A, -B, -C, and -D, which have been detected in cultured normal human keratinocytes and fibroblasts (20). The role of CDH11 in VEGF-D expression has been studied in mouse

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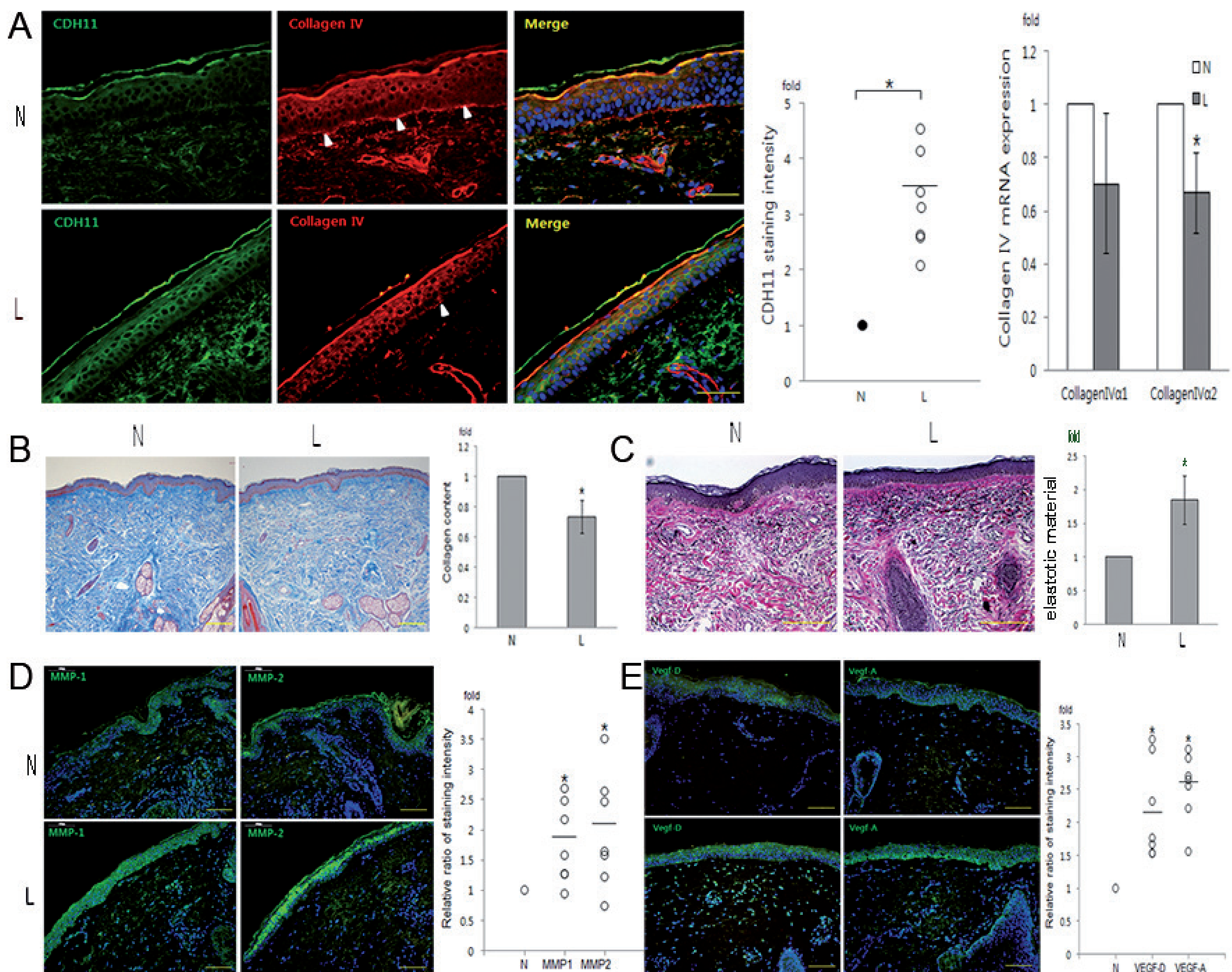

Fig. 1. Correlation of cadherin 11 (CDH11) expression with basement membrane (BM) damage and dermal changes in patients with melasma. Hyperpigmented (lesion; L) and normally pigmented (N) skin from 7 CDH11-upregulated melasma patients. (A) Representative immunofluorescence staining with anti-type IV and -CDH11 antibodies and real-time PCR of type IV (α1 and α2) collagen expression. The CDH11 data in the graph represent the mean ± standard deviation (SD) of staining intensities measured in 3 microscopic fields (×400) (*$p<0.05$). Nuclei were counter-stained with Hoechst 33258 (*bar* = 0.05 mm). *Arrowheads* indicate BM. The data of type IV collagen mRNA expression in the graph represent the mean ± SD of 3 independent experiments (*$p<0.05$). Histochemical staining with (B) Masson's trichrome and (C) Verhoeff. The data in the graphs were measured same as in A (*bar*=0.1 mm). Immunofluorescence staining with (D) anti-MMP-1 and MMP-2 and (E) anti-VEGF-A and VEGF-D antibodies.The data in the graphs were measured same as in A (*bar* = 0.1 mm). MMP: matrix metalloproteinase, VEGF: vascular endothelial growth factor.

fibroblasts (21). Therefore, the effect of CDH11 on the expression of VEGF-D and the parental VEGF molecule, VEGF-A, was examined.

Fibroblasts with CDH11 overexpression increased VEGF-D expression, whereas those with CDH11 knockdown decreased levels of VEGF-D ($p<0.05$, Fig. 3A). CDH11-overexpressing fibroblasts also had stronger immunofluorescence staining with anti-VEGF-D (Fig. 3B). No significant changes in VEGF-A expression were found in fibroblasts, regardless of CDH11 expression (Fig. 3A). On the other hand, CDH11 overexpression in keratinocytes caused an increase in VEGF-A protein expression (Fig. 3C) with a stronger immunofluorescence staining intensity against anti-VEGF-A antibody (Fig. 3D), and CDH11 knockdown caused a decrease in VEGF-A expression ($p<0.05$). CDH11 expression changes in keratinocytes did not lead to any significant changes in VEGF-D expression.

No correlation of UV-induced BM damage/dermal changes with CDH11 expression

In UV-induced photodamaged skin, a decrease in type I and IV collagen with an increase in MMP expression and an increase in VEGF have been found (16, 22–24). The changes induced by CDH11 (Figs 2A, B, D, E–I, 3) were similar to those induced by UV exposure. In comparison, UV-induced changes on the cultured cells were examined using exposure of the cells to varying intensities of NB-UVB (up to 1,000 mJ/cm^2).

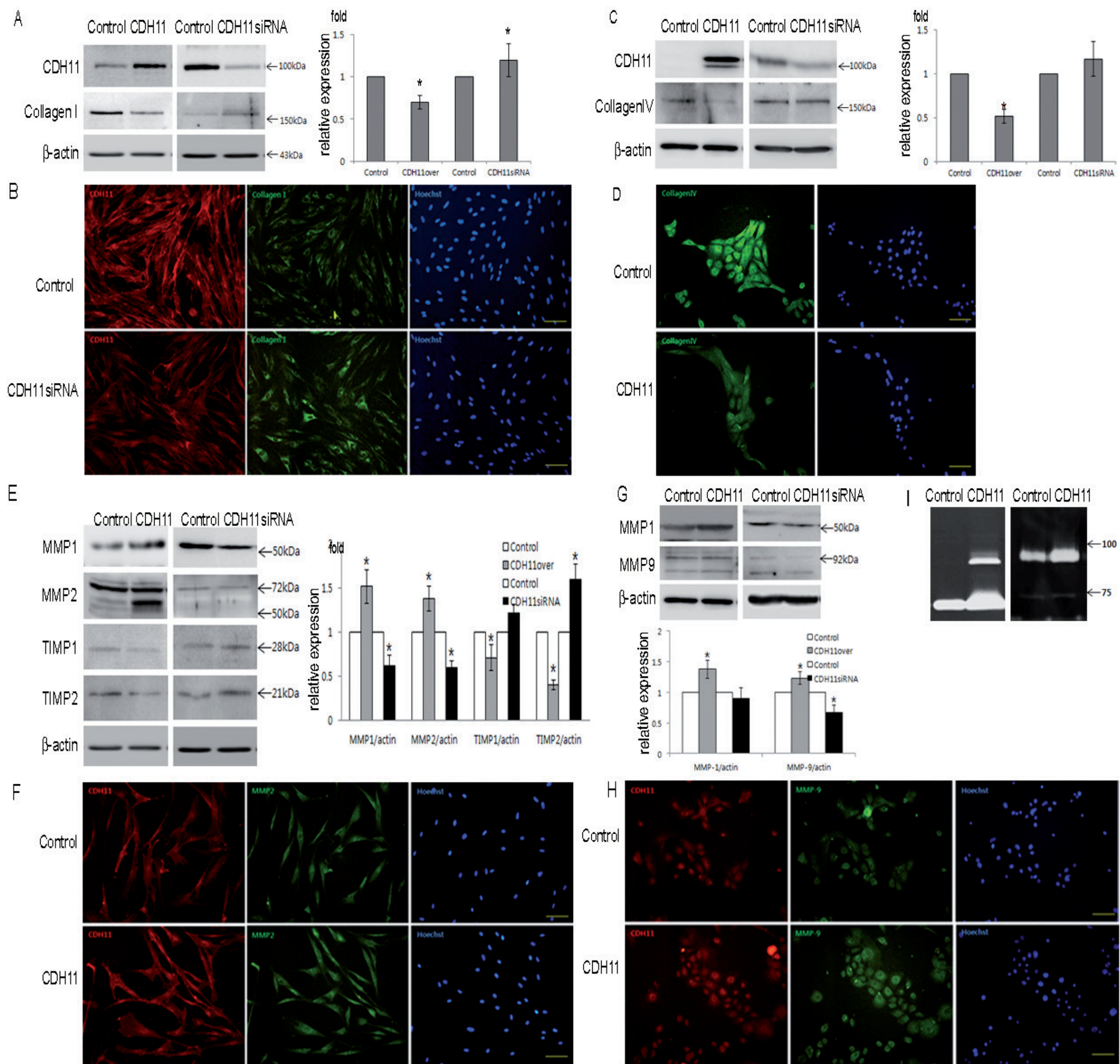

Fig. 2. Effect of cadherin11 (CDH11) on the expression of collagen, matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinase (TIMPs). (A) Western blot analysis and (B) representative immunofluorescence staining for type I collagen expression in primary cultured normal human fibroblasts with or without CDH11 overexpression or knockdown. (C) Western-blot analysis and (D) representative immunofluorescence staining for type IV collagen expression in primary cultured normal human keratinocytes with or without CDH11 overexpression or knockdown. (E) Western blot analysis of MMP (1 and 2) and TIMP (1 and 2) expression and (F) representative immunofluorescence staining using an anti-MMP-2 antibody in fibroblasts with or without CDH11 overexpression or knockdown. (G) Western blot analysis of MMP-1 and MMP-9 expression and (H) representative immunofluorescence staining using anti-MMP-9 antibody in keratinocytes with or without CDH11 overexpression or knockdown. β-actin was used as an internal standard for all Western blot analysis. Data in all graphs represent the mean ± SD of 5 independent experiments ($*p<0.05$). Nuclei were counter-stained with Hoechst 33258 (*bar* = 0.1 mm) in all immunofluorescence studies. (I) Zymogram of MMP-2 and MMP-9 in monolayer-cultured fibroblasts and keratinocytes. MMP: matrix metalloproteinase, TIMP: tissue inhibitor of metalloproteinase.

The expression of collagen type I in fibroblasts and collagen type IV in keratinocytes (Fig. S1A and B[1], respectively) and TIMP1 with TIMP2 in fibroblasts (Fig. S1A[1]) decreased in a dose-dependent manner with increasing intensities of applied NB-UVB, whereas the expression of MMP-1 and MMP-2 in fibroblasts (Fig. S1A[1]) and MMP-1 in keratinocytes (Fig. S1B[1]) increased. Although the applied NB-UVB at these doses induced changes in collagen, MMPs and TIMPs, the irradiation did not increase CDH11 expression in fibroblasts or keratinocytes (Fig. S1A and B[1], respectively).

DISCUSSION

The relationship between melasma and any triggering factor has only been partially identified, and the causative factors may differ for individual patients. It is uncertain how frequently CDH11 upregulation is seen in melasma patient hyperpigmented skin samples. Although the number of patients included in this study was small, the immunofluorescence study and real-time PCR for type IV collagen expression revealed BM disruption in melasma patients with CDH11 upregula-

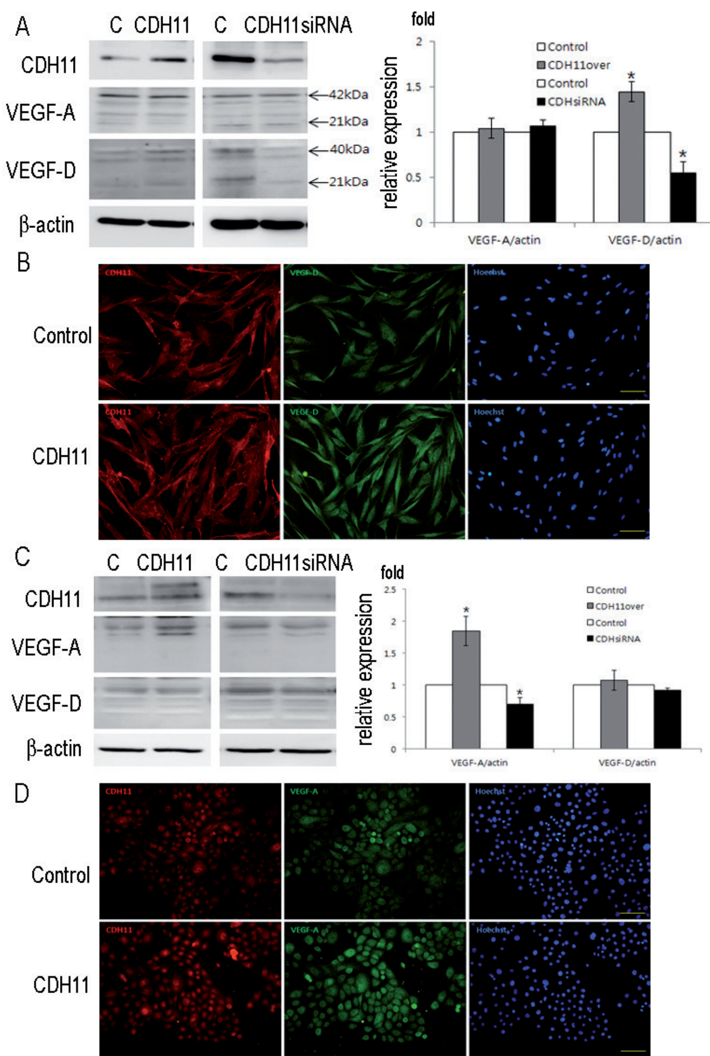

Fig. 3. Effect of cadherin11 (CDH11) on the expression of vascular endothelial growth factors (VEGFs). (A) Western blot analysis of VEGF-A and VEGF-D expression and (B) representative immunofluorescence staining using an anti-VEGF-D antibody in fibroblasts with or without CDH11 overexpression or knockdown. (C) Western blot analysis of VEGF-A and VEGF-D expression, and (D) representative immunofluorescence staining using an anti-VEGF-A antibody in keratinocytes with or without CDH11 overexpression or knockdown. β-actin was used as an internal standard for all Western blot analysis. Data in all graphs represent the mean ± SD of 5 independent experiments (*$p < 0.05$). Nuclei in all immunofluorescence studies were counter-stained with Hoechst 33258 (*bar* = 0.1 mm).

tion (Fig. 1A). The BM, which is composed of type IV collagen in the lamina densa, as well as laminin 5 and type VII collagen, is jointly produced by keratinocytes and fibroblasts. The observation that primary cultured keratinocytes (Fig. 2C and D) and fibroblasts (data not shown) with CDH11 overexpression reduced type IV collagen expression was consistent with the patient samples.

Disruption of BM presumably occurs from increased degradation of BM components without a commensurate increase in their synthesis. The BM could be degraded by MMPs, including MMP-2 (gelatinase A or 72-kDa type IV collagenase) and MMP-9 (gelatinase B or 92-kDa type IV collagenase) (25). An increased MMP-2 and MMP-9 expression by fibroblasts or keratinocytes with CDH11 overexpression, but a decrease in their expression by these cells with CDH11 knockdown (Figs 1D, 2E–I), supported the notion of BM disruption due to increases in CDH11 expression. Despite stronger MMP-2-positive immunofluorescence staining in hyperpigmented epidermis, keratinocytes in the basal layers of the hyperpigmented skin samples were not stained (Fig. 1D). This may explain why no recognizable MMP-2 expression was detected in monolayer-cultured keratinocytes (Fig. 2G and I). In addition, MMPs are tightly regulated by TIMPs (26) with TIMP-2 exclusively interacting with MMP-2 and TIMP-1 with MMP-9 (27). Changes in TIMP-2 and TIMP-1 expression were opposite to those in MMP-2 expression in fibroblasts (Fig. 2E) in addition to undetectable TIMP-1/TIMP-2 expression in keratinocytes. These expression profiles could support a role for MMP-2 and MMP-9 in BM disruption. All the aforementioned results suggest that CDH11 overexpression in fibroblasts and keratinocytes reduced the levels of TIMP-1/TIMP-2 and increased MMP-2/MMP-9 activities, resulting in type IV collagen reduction and BM disruption. One caveat is that these cultured cells did not originate from same anatomical sites (i.e. facial skin from cheek areas) due to the difficulty of obtaining enough skin specimens for culturing.

Abundant elastotic material, detected by Verhoeff staining in hyperpigmented skin, has been reported in a considerable percentage of patients with melasma (2, 3). The melasma patients with CDH11 upregulation also had increased elastotic material staining in the hyperpigmented skin (Fig. 1C). Enzymatic degradation by MMP-1 and MMP-2 has been shown to contribute to the accumulation of elastotic material (17). CDH11 overexpression led to increased expression of MMP-1 along with MMP-2 by fibroblasts or keratinocytes and knockdown of CDH11 had the opposite effect on expression of MMP-1 and MMP-2 (Fig. 2E–2I). This suggests a role for increased CDH11 expression on the accumulation of elastotic material through increased MMP-1 and MMP-2.

Changes in type I collagen have not been observed previously in patients with melasma (2). However, Masson's trichrome staining showed decreased type I collagen expression in hyperpigmented skin (Fig 1B). In addition, CDH11 overexpression decreased type I collagen expression, particularly in fibroblasts, whereas CDH11 knockdown increased levels of type I collagen (Fig. 2A, B). As MMP-1 initiates the degradation of

type I collagen, CDH11-induced changes in MMP-1 (Fig. 2E and G) may support a role for CDH11 in type I collagen degradation, resulting in a reduction in type I collagen in the hyperpigmented dermis of melasma patients with CDH11 upregulation. In addition to BM disruption, dermal collagenolysis could facilitate the *in vivo* role of CDH11 upregulation in melasma, through direct cell–cell adhesion between the dermal fibroblasts and melanocytes.

Another histological change in the hyperpigmented skin of patients with melasma has been an increase in the number of dermal vessels and VEGF expression, as reported (4); however, the specific isoforms of VEGF were not delineated in the study. Immunofluorescence staining in the present study suggests increased expression of VEGF-D in the dermis, and an increase in VEGF-A in the epidermis of hyperpigmented skin (Fig. 1E). In addition, CDH11 overexpression or knockdown in fibroblasts changed VEGF-D, but not VEGF-A expression (Fig. 3A and B). In keratinocytes, however, VEGF-A expression was changed with CDH11 overexpression or knockdown (Fig. 3C and D). Although a CDH11 effect has been reported for VEGF-D, there have been no reports on other VEGF isoforms (VEGF-A, -B, and -C) (21), and the reported changes with CDH11 may not be limited to VEGF-D.

Reductions in collagen levels, excessive elastotic material accumulation, vascular ectasia, and damage to the BM have been reported as characteristic findings in skin exposed to UV radiation (9, 16, 22, 23). Considering that UV exposure has been implicated as one of the main causes of melasma development (6), these changes may support the causality of UV for changes in melasma patients. However, observations that the sites of the hyperpigmented skin were adjacent to the normally pigmented skin, and that both sites were located on the lateral side of the cheek near the hairline areas with some protection from sunlight, suggest a role for factors other than UV exposure in the development of BM and dermal changes in melasma. Given that the role of H19 RNA downregulation in melasma, independent of UV (10), CDH11 as one of its effector targets could be a factor involved in BM damage/dermal changes as well as melanogenesis in melasma, regardless of UV irradiation. In addition, a wide range of NB-UVB irradiation intensities did not increase CDH11 expression in cultured fibroblasts and keratinocytes, even though it led to decreased expression levels of type I and IV collagens (Fig. S1A and B[1], respectively). This observation supports the notion that there is no relation between UV-induced phototoxicity and CDH11. The significance of the reduction of CDH11 expression at the highest dose of NB-UVB is unclear. However, expressions of MMP-1 and MMP-2 were also reduced at that dose (Fig. S1A[1]).

In summary, CDH11 overexpression in fibroblasts and keratinocytes may be involved in BM disruption and dermal changes, such as collagenolysis, elastotic material accumulation and vascular ectasia, in melasma, independent of UV irradiation.

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