

DKK1-Mediated Inhibition of Melasma via activating the MITF/tyrosinase Regulation of Oxidative Stress in Melanocytes

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Abstract

Melasma is a common acquired hyperpigmentary disorder characterized by symmetrical, irregular brown patches on sun-exposed facial areas. Its pathogenesis is closely associated with ultraviolet (UV) exposure, genetic predisposition, and hormonal influences, though the precise mechanisms remain incompletely elucidated. The core pathological feature is the hyperactivation of melanocytes, involving α -MSH/MC1R signaling, MITF-dependent melanogenesis, and dysregulation of the Wnt pathway. In melasma lesions, fibroblasts exhibit upregulated secretion of Wnt agonists and reduced expression of the Wnt inhibitor Dickkopf-1 (DKK1), leading to aberrant activation of the canonical Wnt/ β -catenin pathway, which promotes melanocyte proliferation and melanin synthesis. Oxidative stress is another pivotal mechanism, wherein UV-induced reactive oxygen species (ROS) accumulation disrupts the NRF2 antioxidant system, activates inflammatory factors like NF- κ B, and exacerbates melanin production and transfer. As a natural inhibitor of the canonical Wnt pathway, DKK1 blocks signal transduction by binding to LRP5/6 receptors. It has been shown to inhibit MITF expression and melanogenesis in melanoma, but its role in melasma is unclear. This study hypothesizes that DKK1 may ameliorate melasma by attenuating ROS-mediated activation of the MITF/tyrosinase axis and melanosome transfer in melanocytes. Combining cell models with clinical sample analysis, the study aims to systematically elucidate the multidimensional mechanisms involving oxidative stress, the inflammatory microenvironment, and melanin synthesis regulation. This work seeks to provide a theoretical basis for developing DKK1-targeted, precise therapeutic strategies for melasma, moving beyond the traditional MITF/tyrosinase research framework and exploring novel intervention avenues.

1. Introduction

- Melasma is a prevalent pigmentary disorder affecting the face. Due to its visible nature, it significantly impairs patients' quality of life. The etiology of melasma is multifactorial, primarily involving ultraviolet (UV) radiation, genetic factors, and sex hormones, which interact to drive disease development [1]. Its pathogenesis is complex and not fully understood, leading to therapeutic challenges and high recurrence rates. A comprehensive understanding of the pathological alterations in lesional skin is crucial for developing integrated clinical management strategies.

Hyperactive melanocytes are central to melasma pathogenesis. Compared to perilesional skin, melasma lesions exhibit higher epidermal melanin content [2]. Histologically, lesional melanocytes are larger, more dendritic, and more intensely stained. They contain more organelles, and keratinocytes harbor increased numbers of mature melanosomes. Elevated levels of α -melanocyte-stimulating hormone (α -MSH) and its receptor MC1R in the lesional epidermis further stimulate melanocyte activity [3]. MC1R, a G protein-coupled receptor, is a key regulator of skin pigmentation. Its activation stimulates adenylyl cyclase, increasing intracellular cAMP levels. This leads to phosphorylation of the cAMP response element-binding protein (CREB), which upregulates microphthalmia-associated transcription factor (MITF), ultimately enhancing melanin production [4]. Furthermore, compared to normal skin, fibroblasts in

melasma lesions secrete increased levels of Wnt agonists while showing reduced expression of the Wnt inhibitor DKK1 in both fibroblasts and keratinocytes. This imbalance stimulates melanogenesis and melanosome transfer via the activation of canonical and non-canonical Wnt signaling pathways [5]. Although genetic background and female sex hormones are recognized contributing factors, chronic UV exposure is considered a key trigger [6]. UV radiation generates reactive oxygen species (ROS), and when ROS production exceeds cellular antioxidant capacity, oxidative stress ensues [7]. Growing evidence implicates oxidative stress in melasma development [8–11]. Reports suggest oxidative stress can disrupt ciliogenesis. Specifically, oxidative stress in NRF2-downregulated epidermal keratinocytes impairs ciliogenesis and related processes, which in turn stimulates keratinocyte differentiation, melanin synthesis, and melanosome transfer, culminating in hyperpigmentation [12, 13].

The Wnt/ β -catenin pathway plays a critical role in melanocyte biology. It primarily functions by influencing melanocyte development and activating downstream melanogenic enzymes [14]. Wnt signaling promotes the differentiation of melanocyte precursors. Impairment of this pathway reduces the proliferative and differentiative capacity of melanocytes, a consideration in treatments aiming for repigmentation. Interestingly, different Wnt ligands can have opposing effects. For instance, Wnt5a has been reported to inhibit melanin synthesis, reducing the expression of tyrosinase and tyrosinase-related protein-1 (TRP1) [15]. Conversely, Wnt3a is involved in inducing melanocyte differentiation from stem cells and promotes melanogenesis by upregulating MITF, tyrosinase (TYR), and TRP1 [16, 17]. Furthermore, c-Myc, a target gene of the Wnt/ β -catenin pathway, can mitigate ROS production by activating HIF-1 α , thereby protecting melanocytes from ROS-induced dysfunction and apoptosis. This suggests that modulating the Wnt/ β -catenin pathway could offer novel therapeutic avenues for melasma.

DKK1 is a member of the Dickkopf (DKKs) family of secreted glycoproteins, which includes DKK1, DKK2, DKK3, and DKK4 [18]. Among them, DKK1 is the most extensively studied and is a recognized inhibitor of the canonical Wnt signaling pathway [19]. Park et al. [20] found that DKK1, as a Wnt antagonist, can effectively inhibit melanoma tumor growth. Notably, physiological hypopigmentation in palmar and plantar skin is attributed to the high-level secretion of DKK1 by dermal fibroblasts in these regions [21]. DKK1 inhibits melanogenesis by suppressing the Wnt/ β -catenin pathway in melanocytes [22]. It may also hinder melanin transfer by reducing protease-activated receptor-2 expression in keratinocytes [23]. Additionally, DKK1 can inhibit the growth of normal human melanocytes by downregulating melanocyte-specific markers, including DCT, MART1, TYR, GP100/Pmel17, and MITF [22, 24]. However, its specific role and mechanism in melasma pathogenesis require further investigation.

Based on the above evidence, we hypothesize that DKK1 may inhibit melasma development by regulating melanocyte oxidative stress via the MITF/tyrosinase axis, and thus represents a potential novel therapeutic target. This study aims to explore the role of DKK1 in melasma by integrating mechanisms involving key signaling pathways, oxidative stress, and inflammatory responses.

2. Material and methods

2.1. Cell Culture and Lentiviral Transduction

The immortalized human melanocyte cell line PIG1 (Aorisai Technology Co., ORC1041) was cultured in Roswell Park Memorial Institute (RPMI) 1640 medium (Procell, PM150110) supplemented with 10% fetal bovine serum (FBS, Solarbio, S9020) and 1% penicillin–streptomycin at 37°C in a 5% CO₂ humidified incubator.

To establish a cellular model relevant to melasma pathogenesis, PIG1 cells were exposed to ultraviolet B (UVB) irradiation (300 mJ/cm²). For stable overexpression of DKK1, PIG1 cells were transduced with a lentiviral vector encoding human DKK1 (or a corresponding control vector) following the manufacturer's protocol. Transduced cells were selected with puromycin (1 µg/ml) to generate a stable cell line designated PIG1-DKK1 OE.

2.2. Cell Viability Assay

Cell viability was assessed using the Cell Counting Kit-8 (CCK-8) assay. PIG1 cells were seeded in 96-well plates. At 0, 24, 48, and 72 hours, 10 µL of CCK-8 solution was added to each well. After incubation at 37°C for 2 hours, the optical density (OD) was measured at 450 nm using a microplate reader (Shanghai Sanpu, SP0101C2403071001-150W). Each experiment was performed in triplicate.

2.3. Real-Time Quantitative Polymerase Chain Reaction (RT-qPCR)

Total RNA was extracted from cells using TRIzol. cDNA was synthesized using the SweScript All-in-One RT SuperMix (Wuhan Saiview, G3337). RT-qPCR was performed using 2×Universal Blue SYBR Green qPCR Master Mix (Wuhan Sewell, G3326) on a Applied Biosystems 7500 system. Gene expression levels were normalized to β-actin and calculated using the 2^{-ΔΔCt} method. The primer sequences used are listed in Supplementary Table S1.

2.4. Western Blot Analysis

Total protein was extracted from cells using RIPA lysis buffer (Solarbio, R0010) containing protease and phosphatase inhibitors. Protein concentration was determined using a BCA assay kit (Solarbio, PC0020). Equal amounts of protein were separated by 10% SDS-PAGE gels (Beyotime, P0014D) and transferred to PVDF membranes (Millipore, IPVH00010). After blocking with 5% skim milk for 2 hours at room temperature, membranes were incubated overnight at 4°C with the following primary antibodies: anti-NRF2 (Affinity, AF0639), anti-MITF (Immunoway, YM8062), anti-DKK1 (Affinity, BF8416), and anti-β-actin (Bioss, bs-0061R). Following washes with TBST (Beyotime, ST673), membranes were incubated with appropriate horseradish peroxidase (HRP)-conjugated secondary antibodies (1:10000) for 1 hour at room temperature. Protein bands were visualized using an enhanced chemiluminescence (ECL) substrate and imaged with an automated chemiluminescence imaging system.

2.5. Measurement of Oxidative Stress Markers

The levels of malondialdehyde (MDA, a lipid peroxidation product), superoxide dismutase (SOD, an antioxidant enzyme), and reduced glutathione (GSH, an antioxidant) in cell lysates or culture media were measured. MDA and SOD levels were quantified using specific commercial assay kits (UPLC-MS, UPLC-MS-4417;UPLC-MS-4529) according to the manufacturers' instructions. The GSH level was determined using a commercial GSH assay kit (Elabscience, E-BC-K030-M).

2.6. Intracellular Reactive Oxygen Species (ROS) Detection

Intracellular ROS levels were measured using the fluorescent probe 2',7'-dichlorodihydrofluorescein diacetate (DCFH-DA, Beyotime, S1105S). Cells were incubated with 10 μ M DCFH-DA in serum-free medium at 37°C for 20 minutes. After three washes with PBS to remove excess probe, the fluorescence intensity was measured at an excitation/emission wavelength of 488/525 nm using a fluorescent microplate reader.

2.7. Tyrosinase Activity Assay

Tyrosinase activity was determined by measuring the rate of L-3,4-dihydroxyphenylalanine (L-DOPA) oxidation. Cell lysates were incubated with 0.1% L-DOPA (Macklin, L807435) at 37°C in the dark for 30 minutes. The absorbance of the resulting dopachrome product was measured at 475 nm using a microplate reader.

2.8. Melanin Content Assay

Cellular melanin content was quantified using a NaOH lysis method. Cell pellets were dissolved in 1 mL of 1 M NaOH (Merck, S8045) and heated at 80°C for 2 hours to solubilize melanin. After centrifugation, the absorbance of the supernatant was measured at 400 nm. Melanin content was normalized to the total protein concentration of the cell lysate.

2.9. Statistical Analysis

All data are presented as the mean $\pm$ standard deviation (SD) from at least three independent experiments. Statistical analysis was performed using GraphPad Prism 9.3 software. Differences between groups were analyzed by one-way analysis of variance (ANOVA) followed by an appropriate post-hoc test (e.g., Tukey's test). A p-value of less than 0.05 was considered statistically significant.

3. Result

3.1 DKK1 Overexpression Inhibits Melanogenesis in PIG1 Melanocytes

- To investigate the role of DKK1 in melanogenesis, we established a PIG1 cell model with stable DKK1 overexpression (PIG1-DKK1OE). Successful overexpression was confirmed at the mRNA level by qPCR (Fig. 1A, $p < 0.01$ vs. Control). We first examined the effect of DKK1 on cell proliferation. The CCK-8 assay revealed that UVB irradiation alone significantly inhibited PIG1 cell proliferation

compared to the control ($p < 0.05$). DKK1 overexpression under UVB conditions (UVB+DKK1 OE) led to a further significant decrease in proliferation ($p < 0.01$ vs. UVB). Importantly, this anti-proliferative effect was partially but significantly reversed by co-treatment with the Wnt pathway activator LiCl (UVB+DKK1OE+LiCl, $p < 0.001$ vs. UVB+DKK1 OE) (Fig. 1B).

- We next assessed melanogenic activity. Tyrosinase activity was significantly enhanced by UVB irradiation ($p < 0.0001$ vs. Control). However, UVB+DKK1 OE cells markedly suppressed this UVB-induced tyrosinase activity ($p < 0.01$ vs. UVB). Again, LiCl treatment restored tyrosinase activity ($p < 0.0001$ vs. UVB+DKK1 OE) (Fig. 1C). Consistent with this, cellular melanin content followed a similar pattern (Fig. 1D). These results collectively demonstrate that DKK1 inhibits both the proliferation and melanogenic function of PIG1 melanocytes, effects that are dependent on Wnt/ β -catenin pathway inhibition.

3.2 DKK1 Overexpression Alleviates UVB-Induced Oxidative Stress in PIG1 Cells

- Given the link between oxidative stress and melasma, we investigated whether DKK1's anti-melanogenic effect involves modulation of oxidative status. Using the DCFH-DA probe, we found that ROS levels were elevated in all UVB-exposed groups compared to the control. Notably, the UVB+DKK1 OE group showed significantly lower ROS levels than the UVB-only group ($p < 0.05$), indicating that DKK1 overexpression mitigates UVB-induced ROS generation. As expected, LiCl treatment increased ROS levels back to a high state ($p < 0.01$ vs. UVB+DKK1 OE) (Fig. 2A).
- We further measured key oxidative stress markers. Compared to the control, UVB irradiation and UVB+DKK1OE+LiCl treatment led to substantial depletion of the antioxidants SOD and GSH ($p < 0.01$ for both) and a marked increase in the lipid peroxidation product MDA ($p < 0.01$). In contrast, cells overexpressing DKK1 exhibited significantly higher levels of SOD and GSH, and a trend towards lower MDA, compared to the UVB group (Fig. 2B-D). These findings demonstrate that DKK1 overexpression alleviates UVB-induced oxidative stress in melanocytes, and this protective effect is antagonized by Wnt/ β -catenin pathway activation.

3.3 DKK1 Inhibits the Wnt/ β -catenin-MITF Axis and Modulates NRF2 Expression

- The Wnt/ β -catenin pathway is a key upstream regulator of MITF, the master transcription factor for melanogenesis. NRF2 is a central regulator of the antioxidant response. To explore the molecular mechanism underlying DKK1's effects, we analyzed the expression of these key molecules.
- As expected, DKK1 mRNA and protein levels were significantly upregulated in the DKK1 OE group (Fig. 3A, D). Concomitantly, both mRNA and protein levels of MITF were downregulated in DKK1-OE cells compared to UVB-irradiated controls ($p < 0.001$) (Fig. 3B, D). LiCl treatment reversed this suppression, significantly increasing MITF expression ($p < 0.001$ vs. UVB+DKK1OE). Interestingly, the

mRNA level of NRF2 was upregulated in the UVB+DKK1OE group compared to the UVB group ($p < 0.05$) (Fig. 3C), a trend also observed at the protein level (Fig. 3D). These results suggest that DKK1 inhibits melanogenesis, at least in part, by suppressing the Wnt/ β -catenin-MITF signaling axis, while simultaneously enhancing the expression of the antioxidant regulator NRF2.

4. Discussion

- Melasma (formerly known as chloasma) is a challenging dermatosis with significant psychosocial impact, often causing emotional distress and reducing quality of life. UV radiation is a primary exacerbating factor, not only by directly stimulating melanogenesis but also by inducing oxidative stress and inflammatory responses that create a microenvironment conducive to hyperpigmentation.

Our study provides novel evidence supporting a protective role for the Wnt inhibitor DKK1 against UVB-induced melanogenesis in human melanocytes. We found that stable overexpression of DKK1 in PIG1 cells significantly inhibited cell proliferation, tyrosinase activity, and melanin production, even under UVB stimulation. These anti-melanogenic effects were functionally linked to the Wnt/ β -catenin pathway, as they were substantially reversed by the pathway activator LiCl. This aligns with the established role of canonical Wnt signaling in promoting melanocyte development and function [25, 26] and suggests that the reduced DKK1 expression observed in melasma lesions [5] may contribute to disease progression by unleashing Wnt/ β -catenin activity.

A key finding of this work is the demonstration that DKK1 overexpression alleviates UVB-induced oxidative stress. Oxidative stress is a well-recognized driver of melasma [8–11]. We observed that DKK1-overexpressing cells maintained higher levels of the antioxidants SOD and GSH, produced less MDA, and had lower intracellular ROS upon UVB challenge compared to control cells. This indicates that DKK1 enhances the cellular antioxidant capacity. The subsequent reversal of this phenotype by LiCl strongly implies that DKK1's antioxidant effect is mediated through inhibition of the Wnt/ β -catenin pathway. This connection is intriguing, as Wnt/ β -catenin signaling has complex, context-dependent relationships with oxidative stress. While some studies suggest Wnt activation can promote antioxidant defense (e.g., via c-Myc/HIF-1 α), our data in this specific model of UVB-stressed melanocytes indicate that pathway inhibition by DKK1 is beneficial.

Mechanistically, we linked these phenotypic effects to the regulation of two critical transcription factors: MITF and NRF2. MITF is the central coordinator of melanocyte differentiation and melanogenic gene expression [27, 28]. As hypothesized, DKK1 overexpression led to downregulation of MITF, providing a direct explanation for the observed reduction in tyrosinase activity and melanin synthesis. This suppression was dependent on Wnt/ β -catenin inhibition. Concurrently, we observed an upregulation of NRF2 in DKK1-overexpressing cells. NRF2 is the master regulator of cellular defense against oxidative stress [29]. A positive relationship between MITF and NRF2 has been reported in other cell types, such as retinal pigment epithelium, where MITF regulates NRF2 to manage oxidative damage [30, 31]. Our

data suggest a more complex regulation in melanocytes under UVB stress, where Wnt/DKK1 signaling can differentially modulate MITF and NRF2. This decoupling might represent a protective mechanism where DKK1, by dampening the pro-differentiation/melanogenic signal, simultaneously bolsters the survival-oriented antioxidant response.

DKK1 is a multifunctional secreted protein with roles in cancer, fibrosis, and bone metabolism [32, 33]. In skin biology, it is a key dermal signal for maintaining regional pigmentation patterns, such as the hypopigmentation of palms and soles [21]. Recent studies highlight its paracrine role from fibroblasts in regulating melanocyte function [22, 34]. Our in vitro findings using a melanocyte monoculture system suggest an autocrine/paracrine action of DKK1 on melanocytes themselves. This adds a new layer to its potential function in skin pigmentation disorders.

This study is primarily based on an in vitro melanocyte model. The use of a single cell line (PIG1) and the absence of co-culture with keratinocytes or fibroblasts limit the ability to fully recapitulate the complex epidermal-dermal crosstalk in melasma. Future studies should employ co-culture systems, 3D skin models, and analyze clinical melasma samples to validate the expression and correlation of DKK1, Wnt/ β -catenin activity, oxidative stress markers, and MITF in vivo. Investigating the upstream regulators of DKK1 expression in dermal fibroblasts within melasma lesions is also crucial.

In conclusion, our study demonstrates that DKK1 inhibits UVB-induced melanogenesis and oxidative stress in human melanocytes, likely through a mechanism involving suppression of the Wnt/ β -catenin-MITF axis and potential enhancement of NRF2-mediated antioxidant defense. These findings position DKK1 as a promising molecular target for melasma treatment. Restoring DKK1 function or mimicking its action could offer a novel strategic approach to counteract the key pathological drivers of hyperpigmentation—aberrant Wnt signaling and oxidative stress—providing a rationale for developing more precise and effective therapies.

Abbreviations

ROS
reactive oxygen
SOD
superoxide dismutase
MDA
malondialdehyde
CAT
catalase
GSH
glutathione.

Declarations

Availability of data and materials

The datasets used for the current study are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declare no conflicts of interest.

Funding Declaration

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Author contributions

YYZ: Data curation, formal analysis, investigation, and writing of the original draft. **WYH:** Resources, data curation, and project administration. **XYK:** Data curation, investigation, and methodology. **SQS:** Visualization and methodology. **QY:** Investigation and project administration. **CHW:** Conceptualization, resources, data curation, supervision, funding acquisition, investigation, methodology. All the authors have read and approved the final manuscript.

Data availability statement

The data are available upon request from the authors.

Additional information

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Disclosure of Potential Conflicts of Interest

The authors declare no conflicts of interest.

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Figures

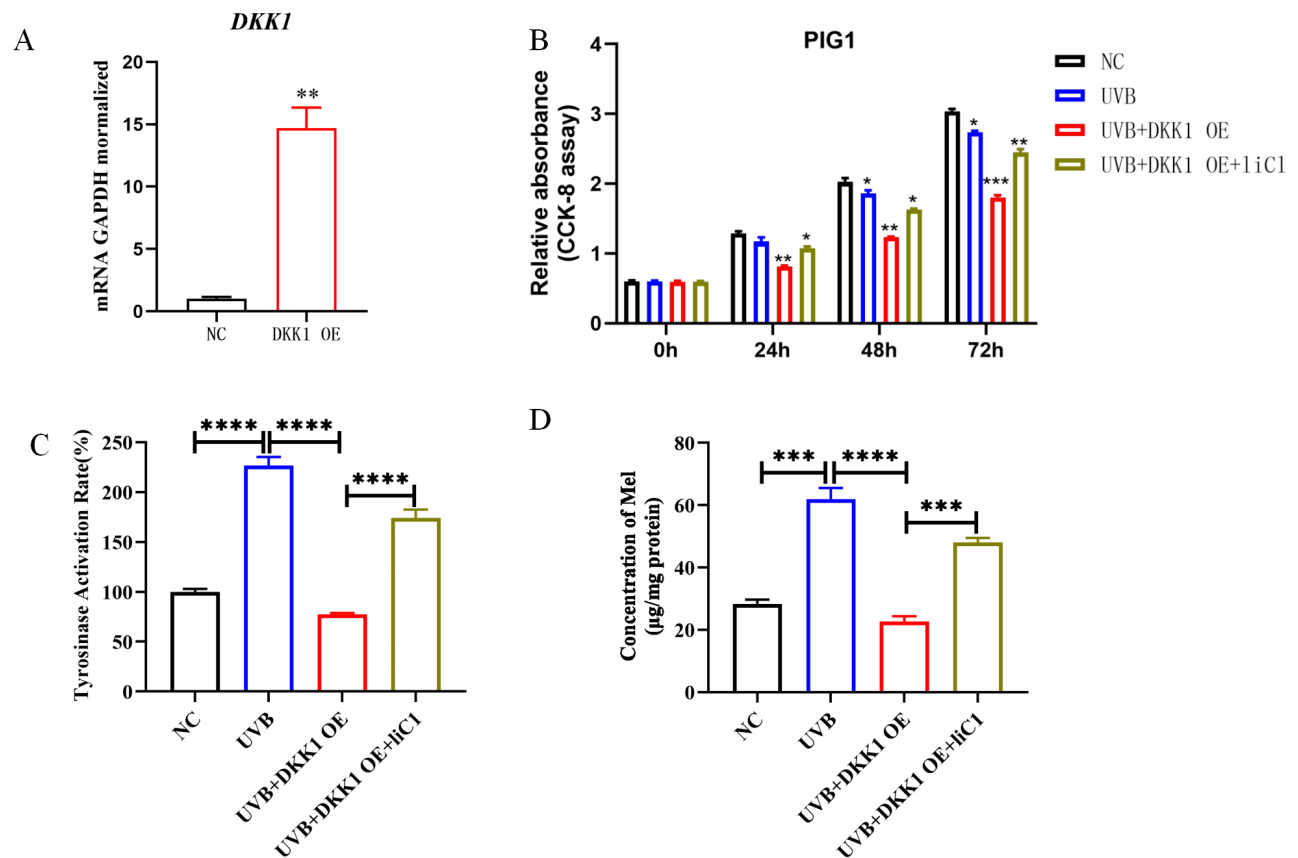


Figure 1

DKK1 overexpression inhibits melanogenesis in PIG1 melanocytes. (A) Validation of DKK1 overexpression in PIG1 cells by qPCR (n=3, **p < 0.01 vs. Control). (B) Cell proliferation assessed by CCK-8 assay (n=3, *p < 0.05, **p < 0.01, ***p < 0.001). (C) Tyrosinase activity measured by L-DOPA oxidation (n=3, ****p < 0.0001). (D) Cellular melanin content (n=3, ***p < 0.001, ****p < 0.0001). Data are presented as mean ± SD.

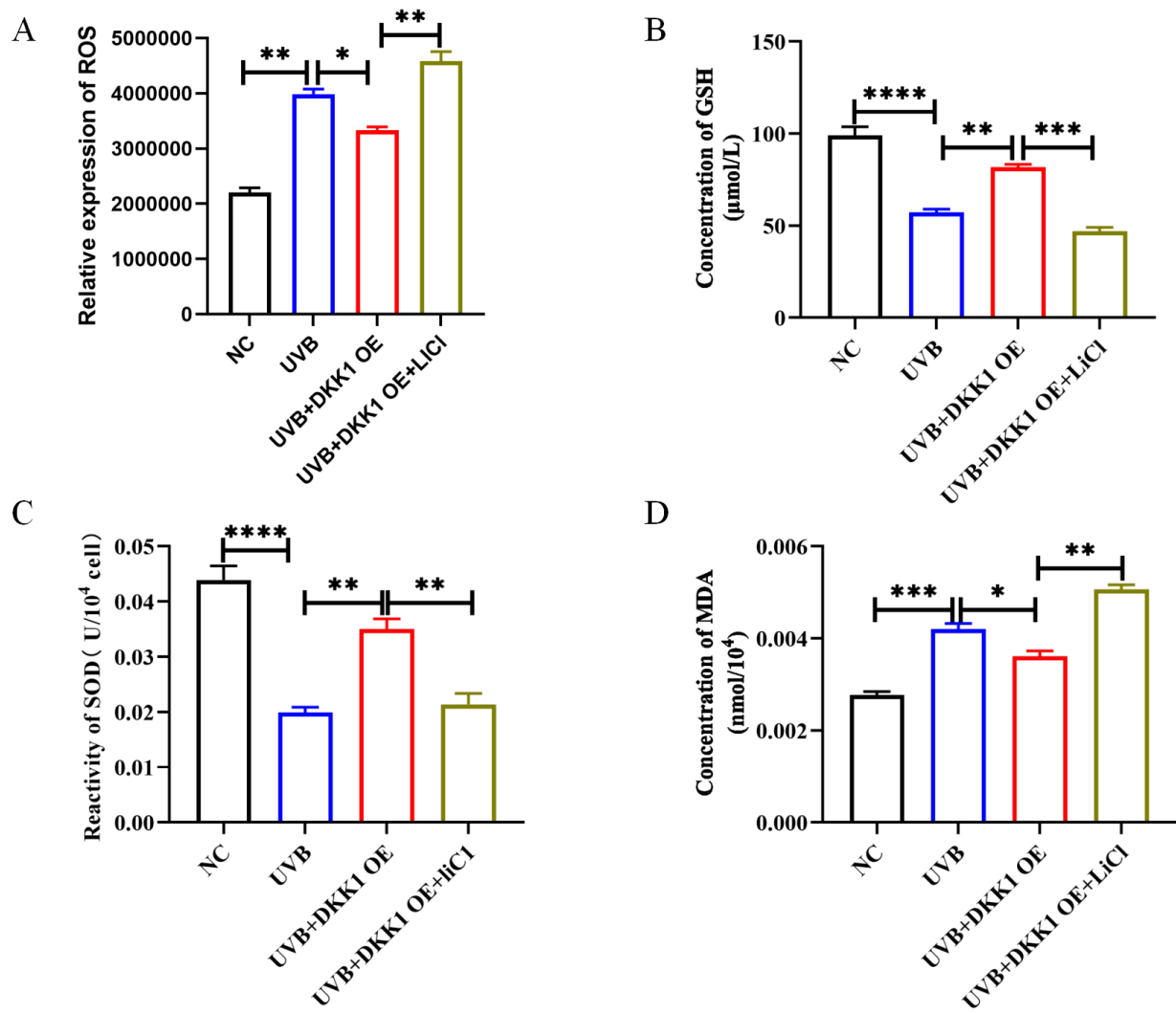


Figure 2

DKK1 overexpression alleviates UVB-induced oxidative stress in PIG1 cells.

(A) Intracellular ROS levels detected by DCFH-DA fluorescence. (n=3, *p < 0.05, **p < 0.01). (B-D) Levels of oxidative stress markers GSH, SOD, MDA in cell lysates/supernatants (n=3, *p < 0.05, **p < 0.01). Data are presented as mean ± SD.

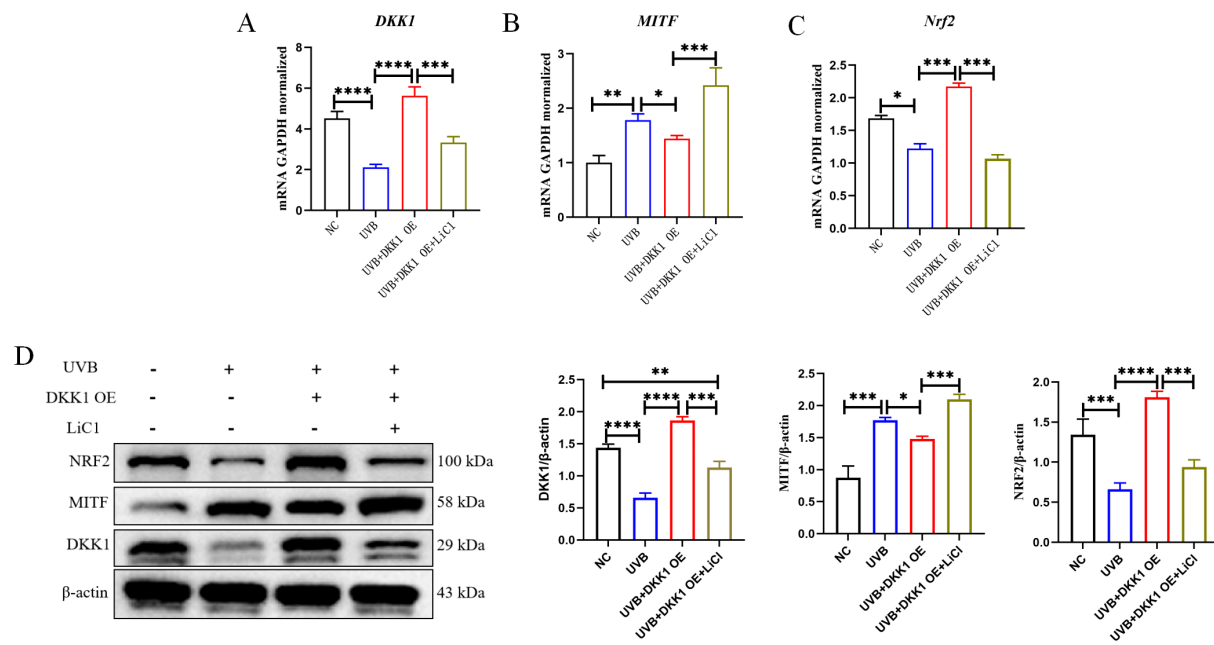


Figure 3

DKK1 inhibits the Wnt/β-catenin-MITF axis and modulates NRF2 expression.

(A-C) mRNA expression levels of (A) DKK1, (B) MITF, and (C) NRF2 determined by qPCR (n=3, *p < 0.05, **p < 0.01, ***p < 0.001). (D) Representative Western blot images and semi-quantification showing protein expression levels of DKK1, MITF, NRF2, and β-actin (loading control). Data are presented as mean ± SD.

Supplementary Files

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