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A Proposal on a New UV-induced Pigmentation Story: Epidermal Keratinocytes Regulate Dermal Fibroblasts-derived Paracrine Factors Involved in Melanin Production of Melanocytes

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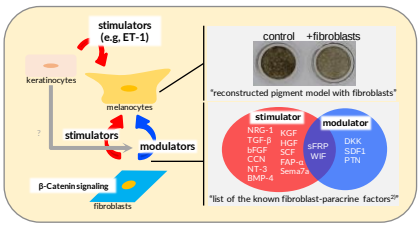
Objectives & Hypothesis:

Recently, there is interest in regulation skin pigmentation thorough fibroblast-paracrine factors. It is well known that keratinocyte-paracrine factors, e.g., Endothelin-1, contribute to UV-induced pigmentation[1]. However, the involvement of the interaction between the dermal fibroblasts and melanocytes in UV-induced pigmentation via epidermal keratinocytes has been uncleared yet.

We recently focused on the Wnt/β-catenin signaling and secretory modulators related to melanogenesis of fibroblasts. It is reported that β-catenin signaling was activated through stimulating of inflammatory cytokines. On the other hands, there are still any unknown points about the relationship between production of modulators (especially DKK1) in fibroblasts and UV-induced pigmentation.



In this study, we considered a hypothesis that keratinocyte-derived inflammatory factors, which are increased by UVB, can activate melanogenesis thorough regulation of fibroblasts secretory modulators such as DKK1.

Results & Summary:

1. Gene expression of Fibroblast-factors (IL-6, MMP-1, DKK1) related to the β-catenin signaling is affected by IL-1α stimulation

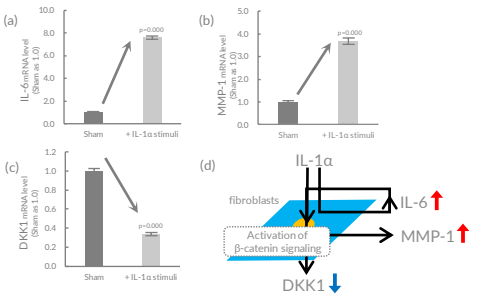


Figure 1. Comparison of the β-catenin signal related genes expression of fibroblasts treated by rhIL-1α Each mRNA level in NHDFs; IL-6 (a), MMP-1 (b), DKK1 (C). Reduction of DKK1 expression through the activation of β-catenin signaling by IL-1α stimuli. It is also known that β-catenin signaling is activated via IL-6, and in addition, MMP-1 expression is induced through β catenin signaling (d).

2. The melanogenesis regulatory function of fibroblasts is affected by UVB through keratinocyte paracrine factors such as IL-1α

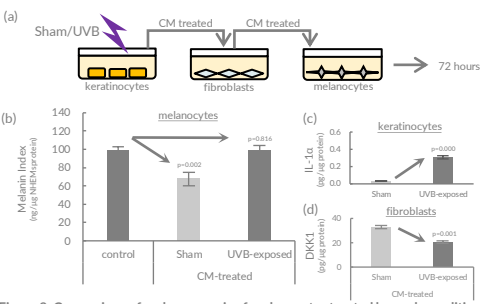


Figure 2. Comparison of melanogenesis of melanocytes treated by each conditioned medium The experiment design (a). Melanin Index in melanocytes treated by each conditioned medium from keratinocyte-fibroblasts, (Sham) and (UVB-exposed) for 72 hours (b). IL-1α secretion in keratinocytes stimulated by UVB (c). DKK1 protein secretion in fibroblasts treated by each conditioned medium of keratinocytes (d).

3. Zinc Glycinate restored DKK1 expression in fibroblasts through suppressing IL1α secretion in UVB-exposed keratinocytes

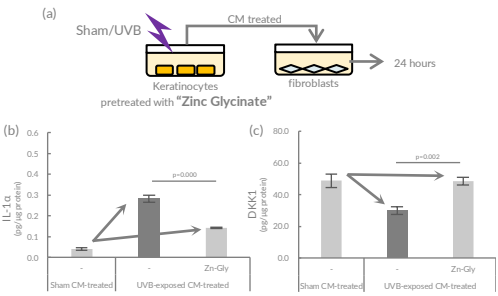


Figure 3. Evaluation of IL-1α in keratinocytes and DKK1 in fibroblasts pretreated with Zinc Glycinate The experiment design (a). Comparison of IL-1α protein level in culture supernatant in keratinocytes (b). Comparison of DKK1 protein secretion in each culture supernatant of fibroblasts (c). In our previous studies, we showed that Zinc Glycinate has a potential for brightening through stimulating metallothionein expression and inhibiting secretion of melanocyte growth and activating factors in keratinocytes[3].

Summary. Our finding showed that the secretion of fibroblast-modulators such as DKK1 involved in pigmentation is regulated thorough keratinocyte-factors such as IL-1α

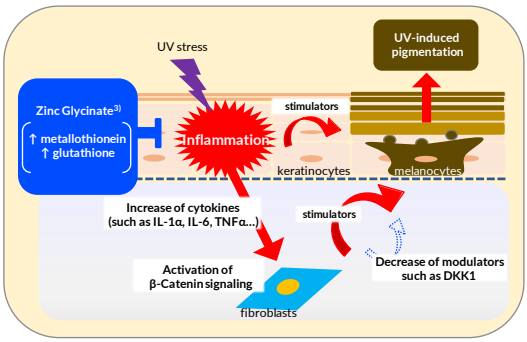


Figure 4. Summary This study and previous studies have shown that inflammatory factors secreted from keratinocytes by UV stimulation can regulate paracrine factors involved in melanin production in fibroblasts. In addition, anti-inflammatory ingredients such as Zinc Glycinate can suppress UV-induced pigmentation.

Conclusión:

In conclusion, the approach about interaction between keratinocytes and fibroblasts may be useful in the prevention of UV-induced pigmentation.

References:

1) Imokawa G, Yada Y, Miyagishi M (1992) Endothelins secreted from human keratinocytes are intrinsic mitogens for human melanocytes. J Biol Chem (34):24675-24680.
2) Upadhyay PR, Ho T, Abdel-Malek ZA. (2021) Participation of keratinocyte- and fibroblast-derived factors in melanocyte homeostasis, the response to UV, and pigmentary disorders. Pigment Cell Melanoma Res (4):762-776.
3) Ochiai Y, Kaburagi S, Okano Y, Masaki H, Ichihashi M, Funasaka Y, Sakurai H (2008) A Zn(II)-glycine complex suppresses UVB-induced melanin production by stimulating metallothionein expression. Int J Cosmet Sci (2):105-12.