MELASMA

REVISIÓN 2016

DRA. ANGELA SEIDEL

ARMENIA

GENERALIDADES

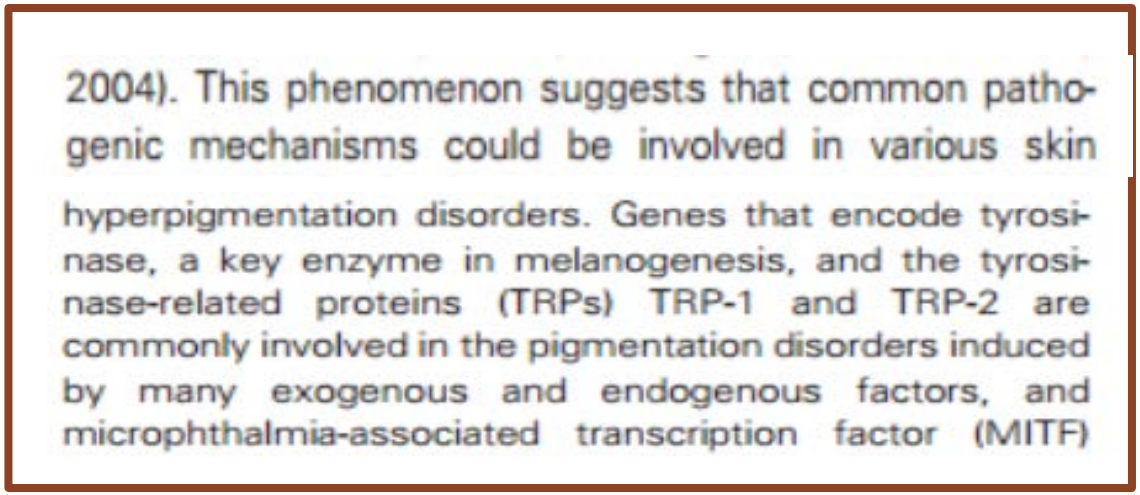
Maculas simétricas en cara.

Genética, radiación UV , hormonas ováricas , tiroideas, embarazo y drogas como fenitoina

Estimulación del mc mediada por Estrógenos

UV : Aumento de melanosomas e hiperplasia focal de Melanocitos. Tanto melanocitosis (número aumentado de melanocitos) como aumento de la melanogénesis (aumento en la producción de melanina)

Cosméticos y fragancias como mecanismo fototóxico : HIPERPIGMENTACION POSTINFLAMATORIA (DERMATITIS DE FOTOCONTACTO) →**inflamación …?**



2004). This phenomenon suggests that common pathogenic mechanisms could be involved in various skin hyperpigmentation disorders. Genes that encode tyrosinase, a key enzyme in melanogenesis, and the tyrosinase-related proteins (TRPs) TRP-1 and TRP-2 are commonly involved in the pigmentation disorders induced by many exogenous and endogenous factors, and microphthalmia-associated transcription factor (MITF)

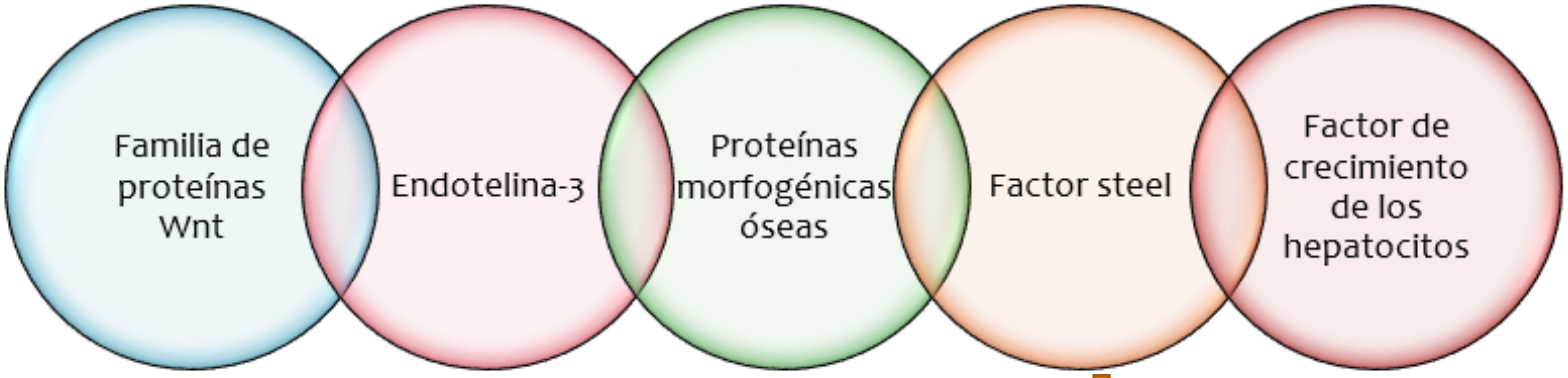
DX DIFERENCIAL

Table 1. Characteristics of melasma versus related hyperpigmentation disorders

Disorder	Characteristic clinical finding	Microscopic finding	Outcome	References
Melasma	Facial pigmentation with centrofacial, malar, and mandibular distribution	Increased melanin in epidermal keratinocytes, dermal macrophages, or both Elastosis, collagen degeneration, and dilated dermal microvasculature	Chronic course with exacerbation	Sanchez et al. (1981), Mandry Pagán and Sánchez (2000), Kang et al. (2002), Grimes et al. (2005), Hernández-Barrera et al. (2008), Kim et al. (2007), Torres-Álvarez et al. (2011)
UV-induced hyperpigmentation	Pigmentation, with wrinkles, tactile roughness, and/or loss of skin tone/ resilience		Normalize after elimination of specific cause	Gilchrest (1996)
Oral contraceptives-induced hyperpigmentation	Similar to those of melasma	Increased melanin in epidermal keratinocytes, dermal macrophages, or both		Resnik (1967), Baker (1969)
Post-inflammatory hyperpigmentation	No specific site predilection, pigmentation on the site of inflammation			Stulberg et al. (2003), Eimpunth et al. (2013)

DESARROLLO EMBRIONARIO

Moléculas de señalización que influyen en la migración de los melanoblastos y su diferenciación a melanocitos



PIEBALDISMO

HTTP://ASOCOLDERMA.ORG.CO/MEDICO/NOTICIAS/REVISION_DE_TEMA_BIOLOGIA_DEL_MELANOCITO

Enzimas y proteínas melanógenas

Tirosinasa	Proteínas relacionadas con la tirosinasa	Proteincinasa C-β
Proteínas estructurales	Proteínas de transporte	Proteínas reguladoras

Melanosom features	Stage I	Stage II	Stage III	Stage IV
				
Shape	Spherical	Elongated	Elliptical, ellipsoidal	Elliptical, ellipsoidal
Internal structure	–	Matrix fibrils are visible	Matrix fibrils are visible	Matrix fibrils are covered by polymerized melanin
TYR	–	+	+	+
TYRP1	–	+	+	+
TYRP2	–	+	+	+
Melanin synthesis	–	–	Begins, settle on internal fibrils	Filled by melanin
Color			Brown	Dark brown to black

Cichorek M., et al. (2013). Skin melanocytes: biology and development. Postepy Dermatologii i Alergologii XXX, 1, 30-4

ESTIMULADORES DE LA MELANOGÉNESIS

PROOPIOMELANOCORTINA

- MSH y ACTH
- Enfermedad de Addison o síndrome de Nelson

ENDOTELINA-1

- Activación de tirosinasa y aumento de niveles TRP-1

FACTOR STEEL

- Inducido por las radiaciones UV
- Regula la melanogénesis y la supervivencia de los melanocitos

MEDIADORES INFLAMATORIOS

- PG y leucotrienos afectan la función de los melanocitos
- Quemadura solar y dermatosis inflamatorias (dermatitis atópica, psoriasis)

NEUROTROFINAS

- Son quimiotácticos para los melanocitos
- Promueven el desarrollo de dendritras

ÓXIDO NÍTRICO

- Aumenta la actividad de la tirosinasa y la melanogénesis

LUZ

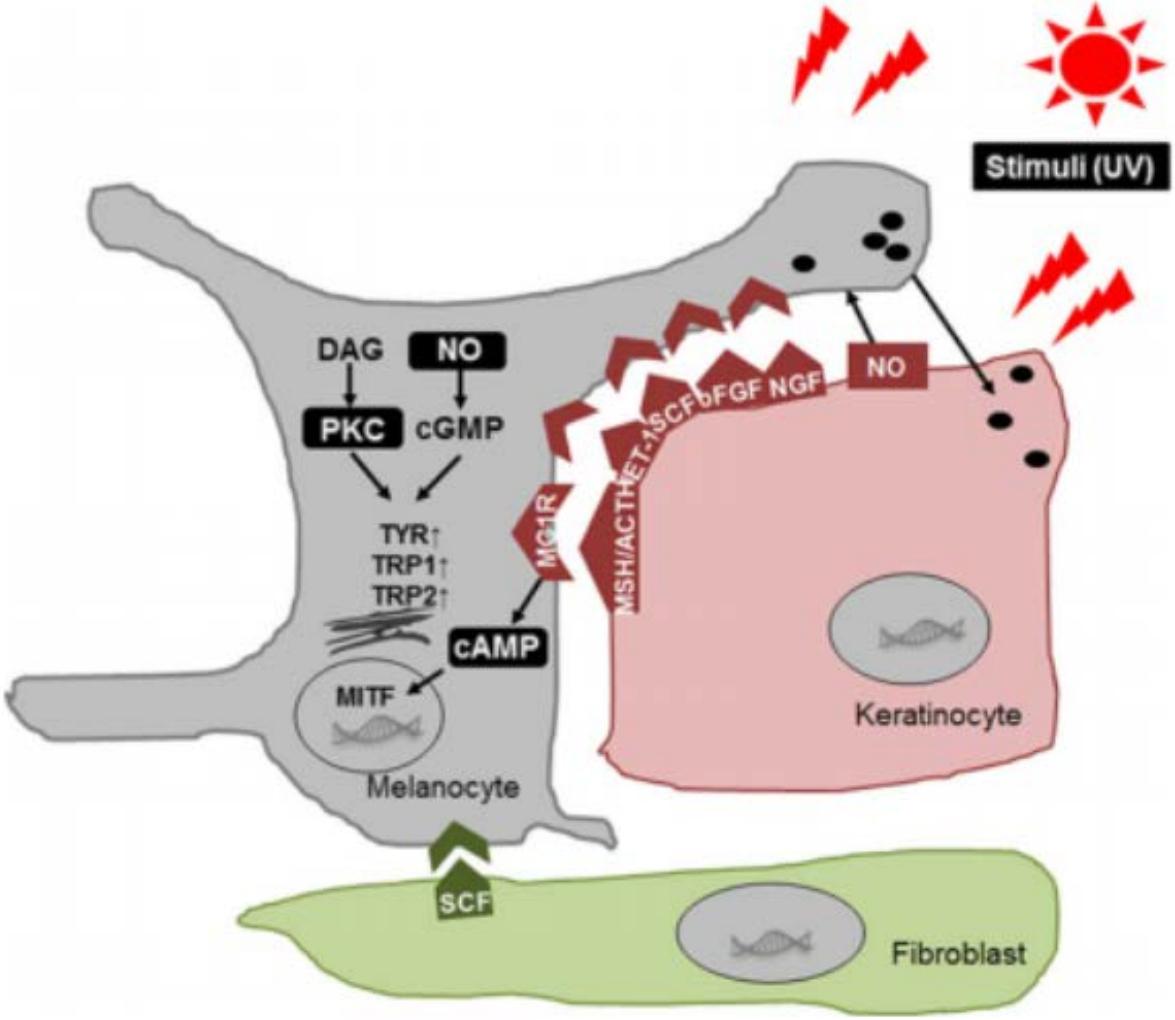
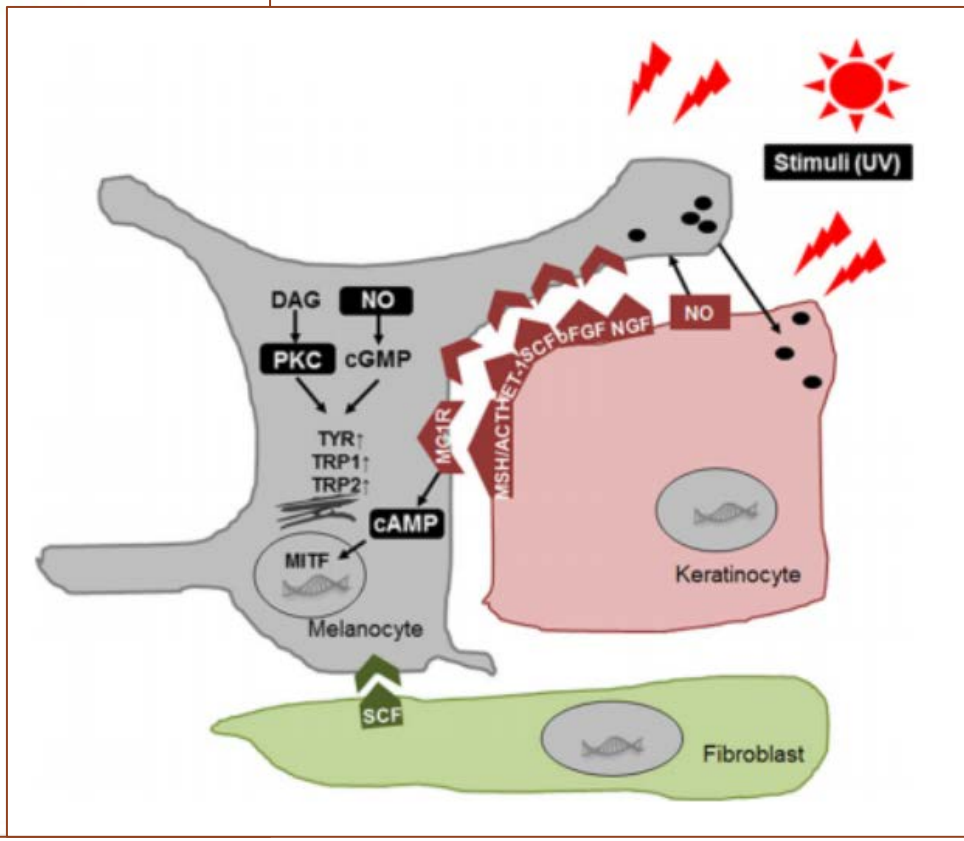


Figure 1. Schematic view of melanogenesis induced by external stimuli, particularly UV radiation. Direct effects on melanocytes and indirect effects on keratinocytes/fibroblasts releasing melanogenic factors, such as proopiomelanocortin (POMC)-derived peptides (MSH, ACTH), ET-1, SCF, bFGF, or NGF, are involved in melanogenesis. Protein kinase C (PKC), NO, and cAMP are major intracellular signal transduction pathways. The black ovals indicate melanosomes (DAG, 1,2-diacylglycerol; NO, nitric oxide; MSH, melanocyte-stimulating hormone; ACTH, adrenocorticotrophic hormone; ET-1, endothelin-1; SCF, stem cell factor; bFGF, basic fibroblast growth factor; NGF, nerve growth factor; MC1R, melanocortin-1 receptor; TYR, tyrosinase; TRP, tyrosinase-related protein).

Table 3. Expression of paracrine melanogenic factors in mel

Origin	Factors
Keratinocytes	Neural endopeptidase
	NGF
	Alpha-MSH
	bFGF
	ET-1
	iNOS
Mast cell	Histamine
Fibroblasts	SCF
	bFGF
	HGF
	KGF
	DKK1
	Neuregulain-1
	VGEF



ESTROGENOS

También progestágenos → estudios contradictorios

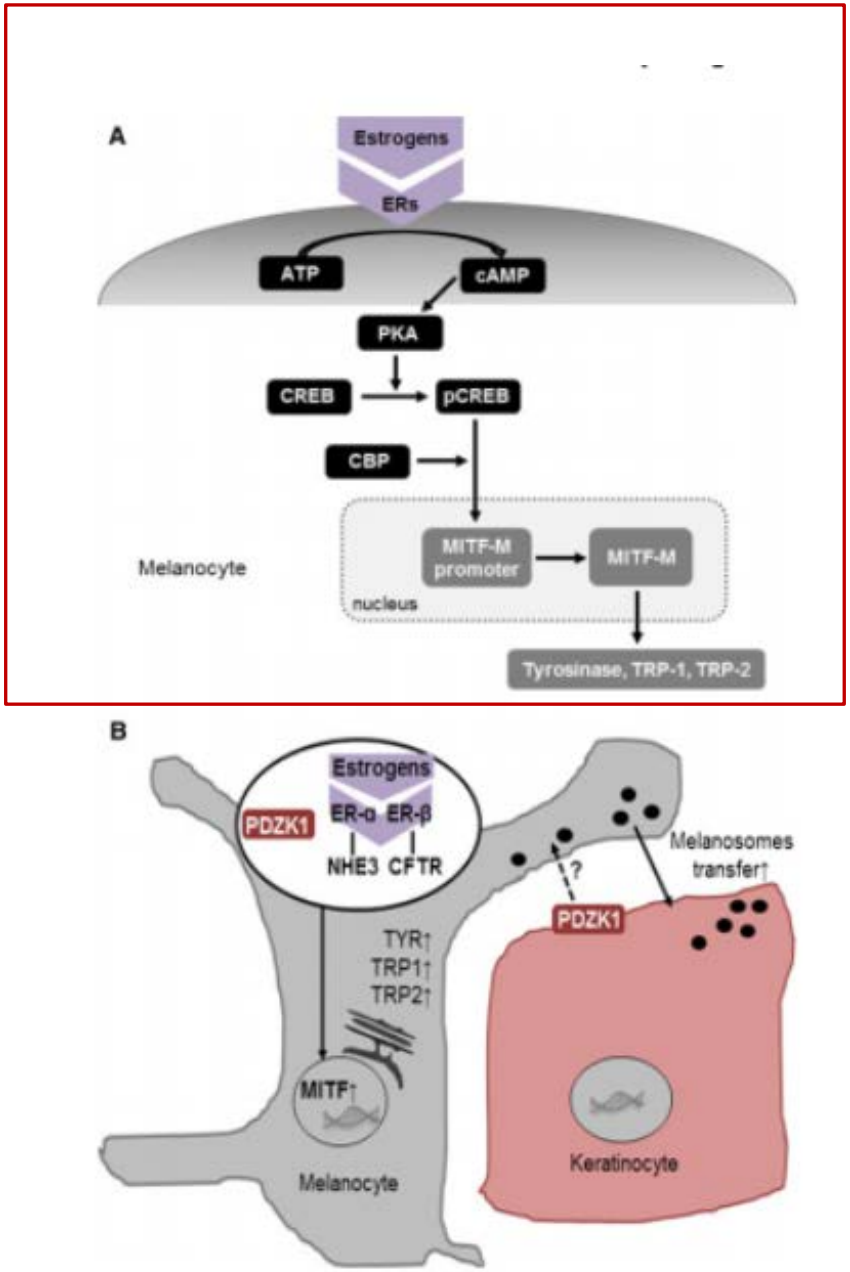


Figure 3. Mechanism involved in estrogen-induced melanogenesis and PDZK1 role in melasma. (A) By binding to ERs, estrogen enhances cAMP levels and upregulates CREB, MITF, and tyrosinase family protein expression, with the involvement of the PKA pathway. (B) PDZK1 could facilitate the estrogen action by interaction with other proteins including ion exchangers, resulting in the stimulation of melanogenesis and melanosome transfer in melasma patients (ER, estrogen receptor; PKA, protein kinase A; CREB, cAMP responsive-element-binding protein; CBP, CREB-binding protein; MITF, micropthalmia-associated transcription factor; TYR, tyrosinase; TRP, tyrosinase-related protein; PDZK1, PDZ domain protein kidney 1; NHE, sodium–hydrogen exchanger; CFTR, cystic fibrosis transmembrane conductance regulator).

or melanocyte–keratinocyte co-cultures. PDZK1 is a member of the sodium–hydrogen exchanger regulatory factor (NHERF) family, called NHERF-3. As estrogen exerts actions through NHERF1 or PDZK1 regulation in ER-containing breast cancer cells (Ediger et al., 1999; Ghosh et al., 2000), estrogen increases PDZK1 with

FACTORES DÉRMICOS

- Fibroblastos
- Mastocitos → Urticaria pigmentosa. H2. ⬆
- Vasculatura

β-CATENINA EN LA VÍA DE SEÑALIZACIÓN WNT/ β-CATENINA

La vía de señalización Wnt/β-catenina juega un papel crucial en la regeneración de tejidos y en el proceso de diferenciación de células madre (8, 9). Esta vía de señalización fue descrita por primera vez en *Drosophila* (mosca de la fruta) y

β-catenina se encuentra en dos complejos moleculares, que corresponden a estas dos funciones: el primero corresponde a β-catenina como parte de complejos de alto peso molecular implicados en la adhesión celular mediada por E-cadherina; en la segunda función, β-catenina, se encuentra en estado monomérico participando en la señalización de la vía Wnt/β-catenina

FIBROBLASTOS

2006; Torres-Álvarez et al., 2011). Meanwhile, we demonstrated that reduced WIF-1 expression in the hyperpigmented skin of melasma patients increases melanognesis and melanosome transfer, irrespective of UV irradiation (Kim et al., 2013a,b). WIF-1, as a secreted antagonist of Wnt signaling, belongs to the secreted Frizzled-related protein class, which inhibits both the canonical and non-canonical Wnt pathway (Hsieh et al., 1999). WIF-1 is expressed in both cultured normal human keratinocytes and fibroblasts, but not in melanocytes. The decreased expression of WIF-1 not only in keratinocytes but also in fibroblasts reduces WIF-1 binding to Wnts in melanocytes, exerting the action through the canonical Wnt/beta-catenin pathway resulting in MITF upregulation and the non-canonical pathway resulting in translocation of nuclear factor of activated T cells (NFAT) to nucleus

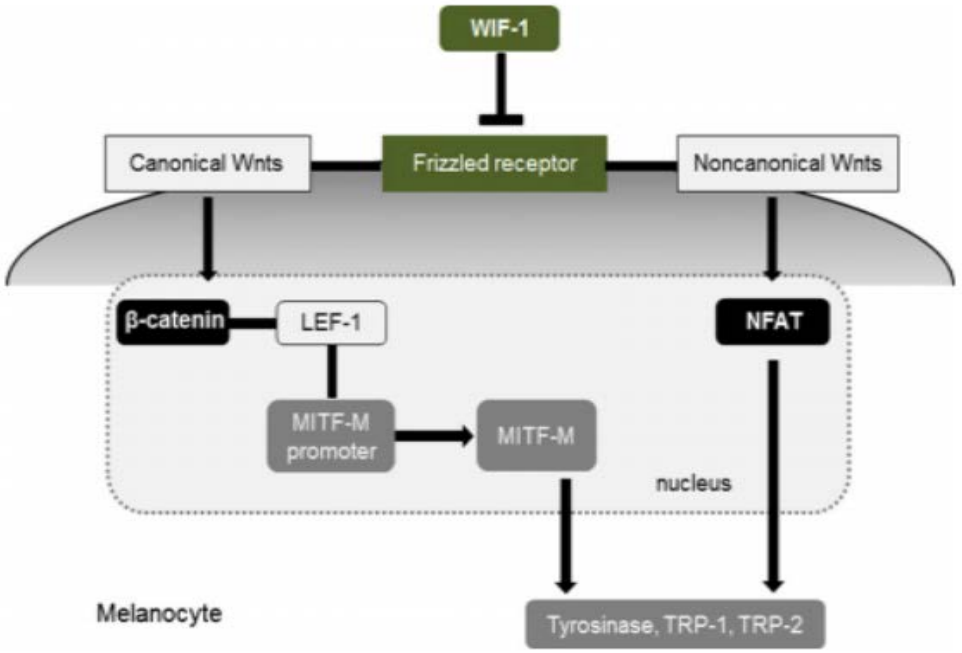


Figure 4. Role of WIF-1 in fibroblasts (or keratinocytes) in melanogenesis. Reduced WIF-1 expression in fibroblasts (or keratinocytes) increases Wnt expression and action in melanocytes through the canonical Wnt/beta-catenin pathway with microphthalmia-associated transcription factor (MITF) upregulation and the non-canonical pathway with NFATc2 translocation to nucleus (WIF-1, Wnt inhibitory factor 1; LEF-1, lymphocyte enhancer binding factor 1; NFAT, nuclear factor of activated T cells).

VASCULATURA

The potential role of altered dermal vasculature has also been considered in melasma patients and UV-irradiated individuals (Yano et al., 2005). Immunohistochemistry data revealed an increase in dermal blood vessel number and vascular endothelial growth factor (VEGF) expression in pigmented lesion of melasma (Kim et al., 2007) (Table 3). Although VEGF can increase the number and diameter of peripheral blood vessels (Chen et al., 2014), the role of VEGF in skin pigmentation has not been clearly elucidated. In addition, the therapeutic outcomes of

MicroRNAs and their targets in melasma development

MicroRNAs (miRNAs) are small, 20–24 nucleotide, endogenously expressed non-coding RNAs. MiRNAs anneal to the 3′ untranslated region of mRNAs in a sequence-specific fashion and then either block translation or promote transcript degradation, thus playing a major role in post-transcriptional regulation of gene expression (Filipowicz et al., 2008). Based on the asso-

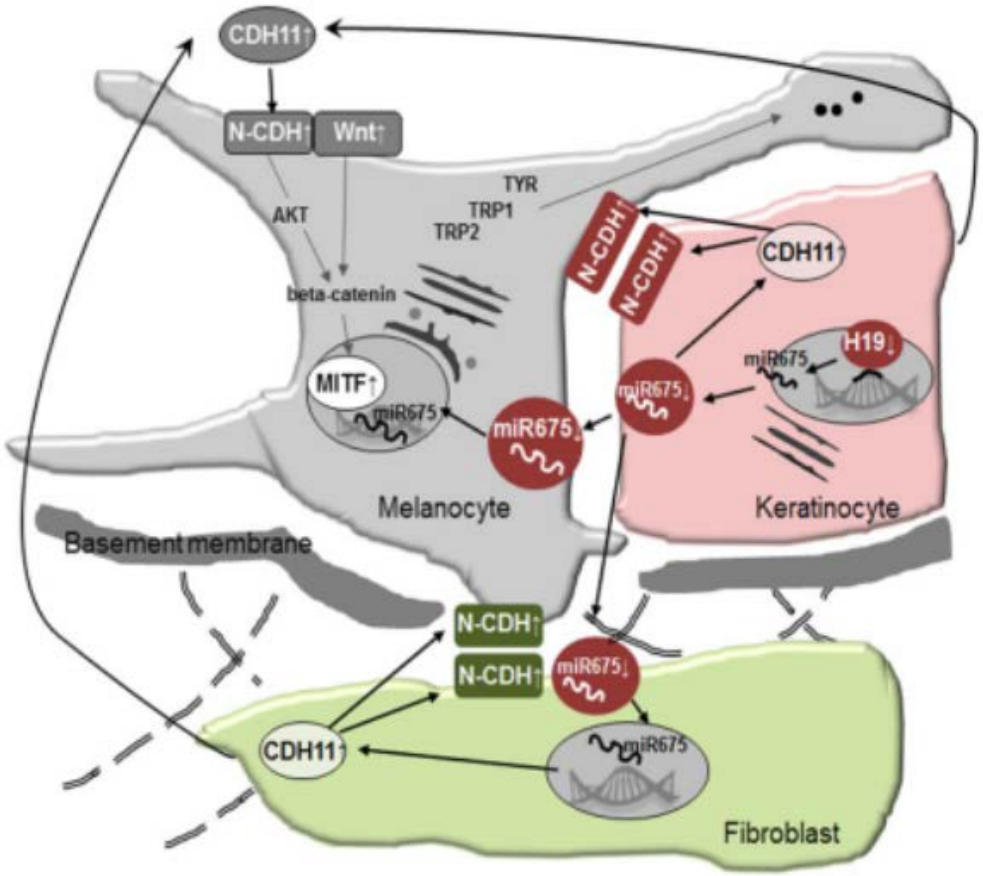


Figure 5. Schematic view of the role of H19-derived miR-675 in keratinocytes in melasma. MiR-675 is delivered from keratinocytes to melanocytes and fibroblasts via membrane-bound exosomes. MiR-675 could exert the action through either microphthalmia-associated transcription factor (MITF) in melanocytes or CDH11 in fibroblasts/keratinocytes as its target. CDH11 in fibroblasts or keratinocytes is involved in melanogenesis via the canonical Wnt and AKT activation pathways in neighboring melanocytes through the induction of N-cadherin (CDH, cadherin; AKT, apoptosis signal-regulating kinase; TYR, tyrosinase; TRP, tyrosinase-related protein).

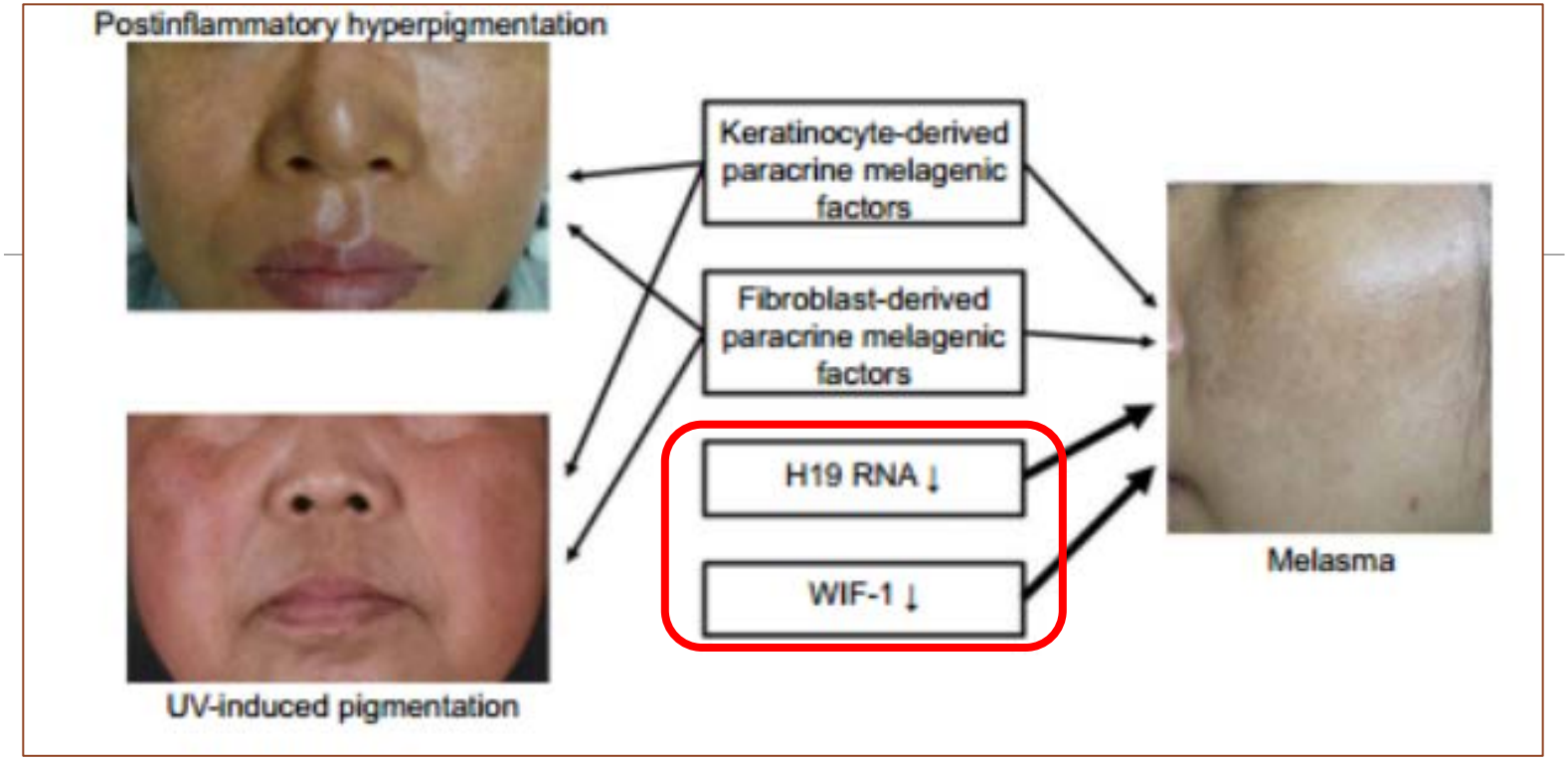


Figure 2. Factors involved in e melanogenesis in melasma versus other hyperpigmentation disorders. Decreased expression of H19 RNA and WIF-1 is involved in the pathogenesis of melasma, but not post-inflammatory hyperpigmentation and UV-induced pigmentation (WIF-1, Wnt inhibitory factor 1).

RESUMEN

- Muchos genes relacionados con la biosintesis de melanina, así como marcadores de melanocitos como TYR, MITF, SILV y TYRP1 están **aumentados** en la piel con melasma.
- Los genes de la vía de modulación WNT, están involucrados en la síntesis de prostaglandinas y metabolismo de los ácido grasos.
- El gen H19 transcribe el ácido ribonucleico (RNA) y se ha encontrado **disminuidos** en las lesiones de melasma. Esto induce la estimulación de la **melanogenesis** y aumenta la transferencia de melanina de los melanocitos a los queratinocitos.
- Las vías iNOS y Factor nuclear kappa B → están aumentados en las lesiones de Melasma.
- El proceso biológico más afectado en le Melasma es el **metabolismo de los lípidos**. Los genes involucrados en el metabolismo de los lípidos, como el del peroxisome proliferator-activated receptor alpha (PPAR), arachidonate 15- lipoxygenase, PPAR gamma coactivator 1 alpha, type B (ALXO 15B), diacylglycerol o-acyltransferase 2-like 3 fueron encontrados **disminuídos**. Esto es producido por la exposición crónica de luz UV.

RESUMEN

- Otro cambio visto en el Melasma es el adelgazamiento del **estrato córneo** , y en las biopsias se evidencia aplanamiento de las crestas y adelgazamiento epidérmico.
- En un estudio de Lee *et al*., el índice de melanina, índice de eritema, y la hidratación del estrato córneo estaban **vascularización prominente** que acompaña la hiperpigmentación .
- La exposición prolongada a la luz UV induce inflamación dérmica y activación de los fibroblastos , los cuales pueden aumentar los factores de las células madre en la dermis con Melasma, causando melanogénesis.

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Gene Expression Profiling in Melasma in Korean Women

Microarray en tejido de piel lesional y no lesional 5 mujeres.
334 genes con diferencias →

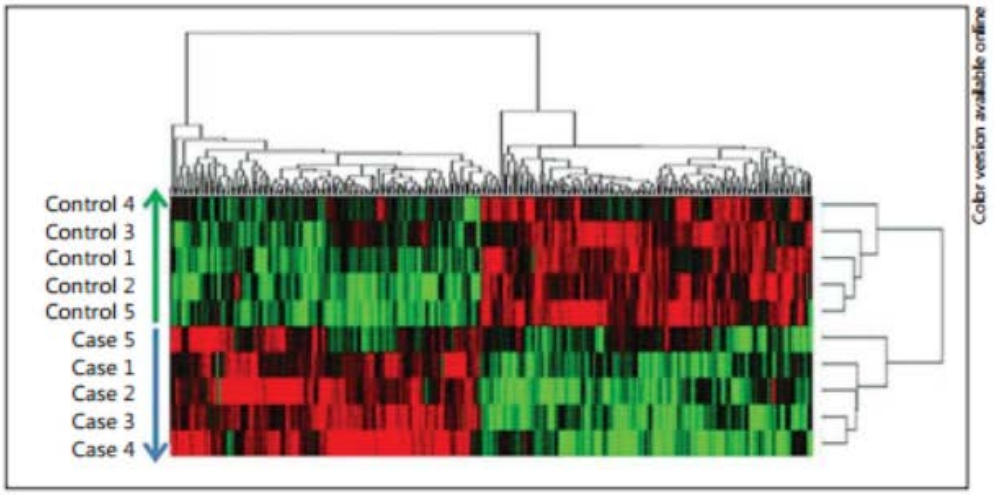

Fig. 1. Hierarchical clustering. A total of 334 genes showed a significant difference in the degree of expression between melasma lesional skin and normal adjacent one ($p < 0.05$) (fold modulation >1.4 or <0.71). We performed a hierarchical clustering analysis of these 334 genes, thus showing that 34 of them showed a >2-fold change in the degree of expression in melasma lesional skin compared with normal adjacent one. A scale bar represents changes in color depending on the log-transformed expression level.

- ADIPOQ disminuido: Adiponectina rel con PPAR-g : muy relacionado con melanogenesis. Con cicatrización de heridas y posiblemente con función de barrera

- Cambios en genes de función de barrera aumento 2v.

- GDA (GUANIN DEAMINASA . Enzima muy importante en todas las cel . Iniciador en síntesis de purinas) Tiene que ver con el desarrollo neural y de dendritas. Aumento 9 v.

- Vía WIF 1/Wnt . Disminuida.

- Genes del Mb de Estrógenos : aumentados .

Traditionally, Wood's lamp examination is done to identify the location of pigment, but is limited to epidermal melasma and cannot be used reliably in Fitzpatrick skin types V and VI as dark-skin melanin pigmentation obscures the detection of dermal melanin [19]. Melasma is reliably graded on the basis of area and severity parameters [i.e., melasma area and severity index (MASI) score] [20, 21].

Table 1 Classification of depigmenting agents and their mechanism of action [16–18]

Stage of melanin synthesis	Deposition	Active molecules
Before melanin synthesis	Tyrosinase transcription	Tretinoin, c-2 ceramide
	Tyrosinase glycosylation	$PaSSO_3Ca$
	Inhibition of plasmin	Tranexamic acid
During melanin synthesis	Tyrosinase inhibition	Hydroquinone, mequinol, azelaic acid, kojic acid, arbutin, deoxyarbutin, licorice extract, rucinol, 2,5-dimethyl-4-hydroxy-3(2H)-furanone, *N*-acetyl glucosamine, resveratrol, oxyresveratrol, ellagic acid, methyl gentisate, 4-hydroxyanisole
	Peroxidase inhibition	Phenolic compounds
	Reactive oxygen species scavengers	Ascorbic acid, ascorbic acid palmitate, thiotic acid, hydrocumarins
After melanin synthesis	Tyrosinase degradation	Linoleic acid, α-linoleic acid
	Inhibition of melanosome transfer	Niacinamide, serine protease inhibitors, retinoids, lecithins, neoglycoproteins, soybean trypsin inhibitor
	Skin turnover acceleration	Lactic acid, glycolic acid, linoleic acid, retinoic acid
	Regulation of melanocyte environment	Corticosteroids, glabiridin
	Interaction with copper	Kojic acid, ascorbic acid
	Inhibition of melanosome maturation	Arbutin and deoxyarbutin
	Inhibition of protease activated receptor 2	Soybean trypsin inhibitor

HOME SEARCH The New York Times

U.S.

Dr. Albert M. Kligman, Dermatologist, Dies at 93

By DENISE GELLENE FEB. 22, 2010

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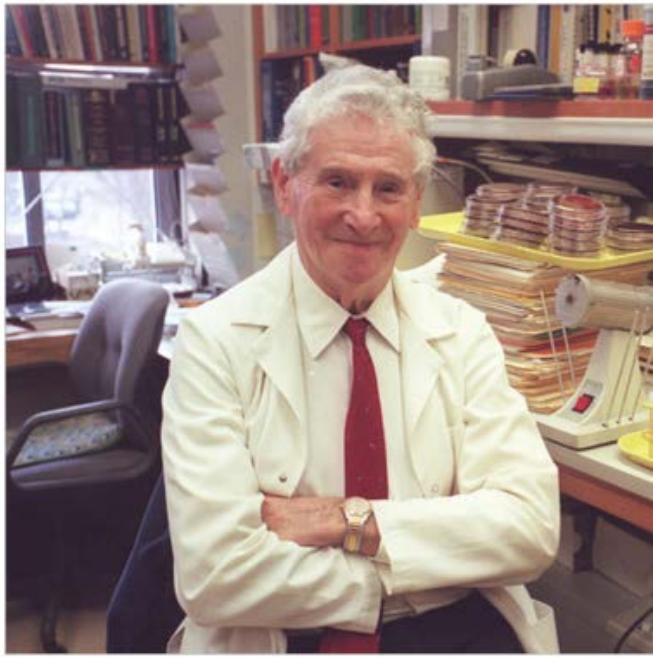
Dr. Albert M. Kligman, a dermatologist who invented the widely used acne medication Retin-A but whose experiments involving prisoners raised ethical questions that dogged his career, died Feb. 9 in Philadelphia. He was 93.

Albert Montgomery Kligman was born in Philadelphia on March 17, 1916, the son of Jewish immigrants. His father, born in Ukraine, was a newspaper distributor; his mother, born in England, was a sales clerk.

His family was poor, but he made his way to college with financial help from Simon Greenberg, a prominent conservative rabbi whom Dr. Kligman had met through a high school friend. He received a bachelor's degree from Pennsylvania State University in 1939 and a doctorate in botany from the University of Pennsylvania in 1942. He studied fungi and wrote a handbook about mushrooms.



Dr. Albert M. Kligman taught at the University of Pennsylvania.
Salvatore C. Dimarco Jr. for The New York Times

Mahmoud *et al*. studied the impact of long-wavelength ultraviolet A (UVA) and visible light on melanocompetent skin.[14] They found that both UVA and visible light were able to increase pigmentation especially in patients with dark skin (skin type IV-VI). Furthermore, pigmentation was more intense and stable after visible light compared to UVA. The study shows that visible light can also induce skin hyperpigmentation, emphasizing the need to use physical sunscreens to prevent melasma relapses.

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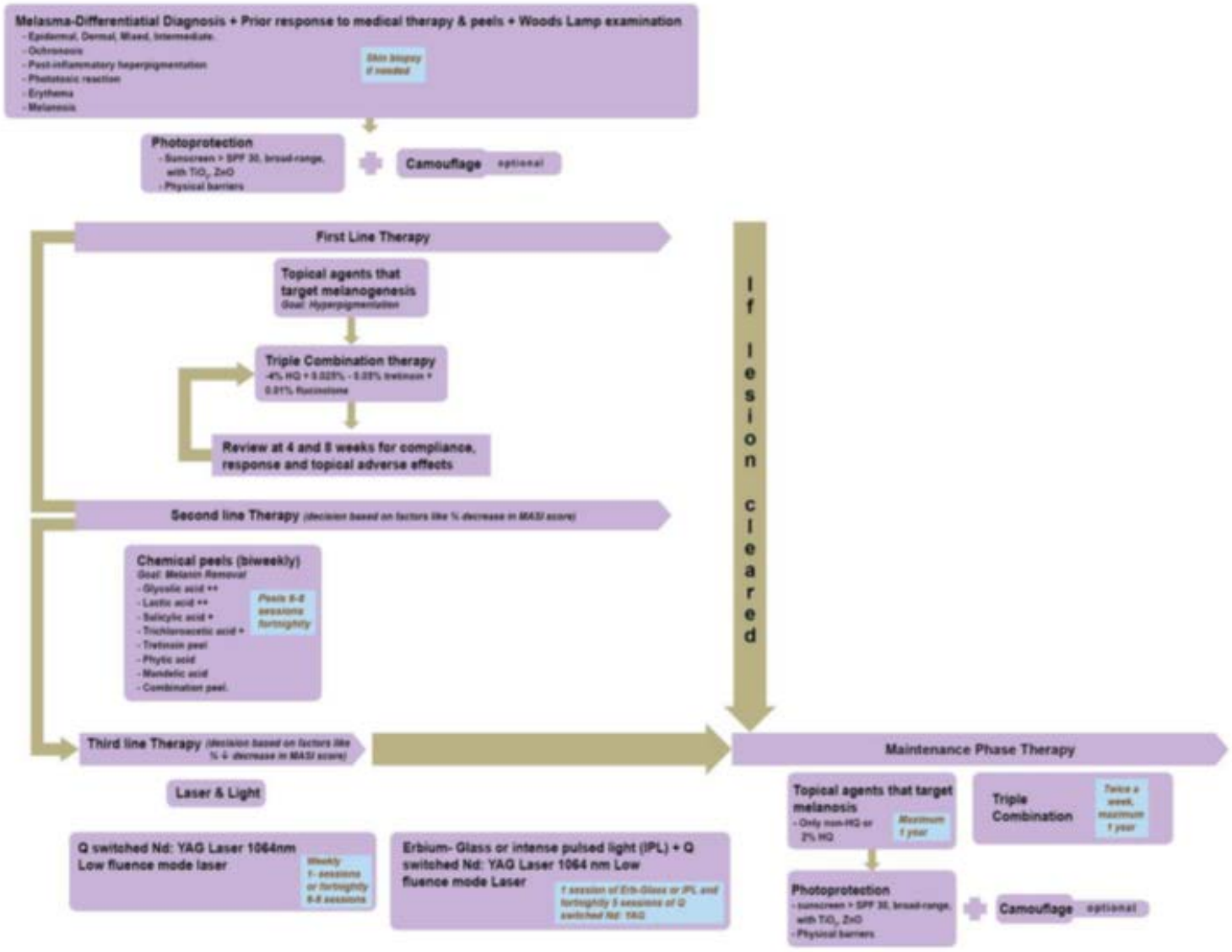
Melasma-Differentiatial Diagnosis + Prior response to medical therapy & peels + Woods Lamp examination
- Epidermal, Dermal, Mixed, Intermediate.
- Ochronosis
- Post-inflammatory hyperpigmentation
- Phototoxic reaction
- Erythema
- Melanosis
Skin biopsy if needed
Photoprotection
- Sunscreen > SPF 30, broad-range, with TiO2, ZnO
- Physical barriers
Camouflage optional
First Line Therapy
Topical agents that target melanogenesis
Goal: Hyperpigmentation
Triple Combination therapy
-4% HQ + 0.025% - 0.05% tretinoin + 0.01% fluocinolone
Review at 4 and 8 weeks for compliance, response and topical adverse effects
Second line Therapy (decision based on factors like % decrease in MASI score)
Chemical peels (biweekly)
Goal: Melanin Removal
- Glycolic acid ++
- Lactic acid ++
- Salicylic acid +
- Trichloroacetic acid +
- Tretinoin peel
- Phytic acid
- Mandelic acid
- Combination peel.
Peels 6-8 sessions fortnightly
Third line Therapy (decision based on factors like % ↓ decrease in MASI score)
Laser & Light
Q switched Nd: YAG Laser 1064nm Low fluence mode laser
Weekly 1- sessions or fortnightly 6-8 sessions
Erbium- Glass or intense pulsed light (IPL) + Q switched Nd: YAG Laser 1064 nm Low fluence mode Laser
1 session of Erb-Glass or IPL and fortnightly 5 sessions of Q switched Nd: YAG
If lesion cleared
Maintenance Phase Therapy
Topical agents that target melanosis
- Only non-HQ or 2% HQ
Maximum 1 year
Triple Combination
Twice a week, maximum 1 year
Photoprotection
- sunscreen > SPF 30, broad-range, with TiO2, ZnO
- Physical barriers
Camouflage optional

Table 10 Bad prognosis factors

Factors that govern negative treatment outcome
Phenotype III–VI: dark hair and/or dark skin
Genetic and familial predisposition [3, 6, 8–10]
Long-term melasma in spite of ≥2 years of treatment
History of procedural interventions
Treated by ≥2 physicians
Long-term self-treatment with steroids [46, 47]
Ochronosis [76, 114]
Mixed-type melasma [115]

TRANEXAMIC ACID SUPPRESSES ULTRAVIOLET B EYE IRRADIATION-INDUCED MELANOCYTE ACTIVATION

Keiichi Hiramoto[1], Yurika Yamate[1], Daijiro Sugiyama[2], Yumi Takahashi[2], Eiichi Mafune[2]

[1] Department of Pharmaceutical Science, Suzuka University of Medical Science
[2] R&D Department, Daiichi Sankyo Healthcare CO., LTD

Introduction

Tranexamic acid (trans-4-aminomethylcyclo- hexanecarboxylic acid) is a medicinal amino acid used in skin whitening care. This study examined the effects of tranexamic acid on the melanocyte activation of the skin induced by an ultraviolet (UV) B eye irradiation. In addition, we also examined sex difference.

Conclusion

These results clearly indicate that tranexamic acid decreases the expression of PC2, which cleavages from proopiomelanocortin to α-MSH in the pituitary gland, thereby suppressing melanocyte activation.

The authors have declared no conflicting interests.

E-mail: hiramoto@suzuka-u.ac.jp

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