S-7 [14:30-15:00]

Trends in the development of whitening agent

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Increased production and accumulation of melanins characterize a large number of skin diseases, which include acquired hyperpigmentation, such as melasma, postinflammatory melanoderma, solar lentigo, etc.. Epidermal and dermal hyperpigmentation can be dependent on either increased numbers of melanocytes or activity of melanogenic enzymes. Ultraviolet light, chronic inflammation and rubbing of the skin as well as abnormal a-melanocyte stimulating hormone (a-MSH) release or other releasing cytokines are triggering factors for these disorders. As a result of their prevalent localization in photo-exposed areas, acquired hyperpigmentation have psychosocial and cosmetic relevance, and many efforts have been devoted to screening recognized and putative depigmenting agents. Moreover, as bleaching compounds are fairly ineffective on derma accumulation of melanin, physical therapies, such as lasers, have been proposed and are currently under investigation.

The knowledge of melanocyte biology and processes underlying melanin synthesis has made remarkable progresses over the last years opening new paths in the pharmacologic approach to the treatment of hyperpigmentation. The pathogenetic mechanisms underlying acquired hyperpigmentation have not been completely clarified, and the therapeutic approaches are focused on the outcome of the process. Numerous are the candidate depigmenting agents and, deeper studies and clinical trials are needed to assess their safety. Recent molecules, even if very promising, need extended follow-up and could disclose undesired effects, not yet identified, or secondary effects, which may accompany the main function. The diverse sites of action lead to a difficult comparison of their efficacy.

This review reports various cause of hyperpigmentation and different approaches to achieve depigmentation, whitening agents used in the markets and promising targets for developing new molecules.

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- Melanogenesis
- Biological targets and whitening agents
- Recent Trends

Skin Disorder

Table I. Common dermatologic diagnoses in black, Hispanic, and Asian racial groups

Black (%)		Hispanic (%)*		Asian†
Acne vulgaris	27.7	Acne	20.4	Xerosis
Eczema	20.3	Eczema	19.3	Pruritus
Pigmentary disorders	9.0	Photoaging	16.8	Nummular dermatitis
Seborrheic dermatitis	6.5	Pigmentary disorders	14.2	Dyshidrosis
Alopecias	5.3	Tinea/onychomycosis	9.9	Atopic dermatitis
Fungal infections	4.3	Condylomata/warts	7.1	Melasma
Contact dermatitis	3.1	Seborrheic keratosis	4.5	Photodermatoses
Warts	2.4	Acrochordons	4.2	Psoriasis
Tinea versicolor	2.2	Seborrheic dermatitis	3.2	Vitiligo
Keloids	2.1	Alopecia	2.3	Lichen amyloidosis (South Asian)
Pityriasis rosea	2.0	Psoriasis	0.8	Nevus of Ito
Urticaria	2.0			Nevus of Oto
				Mongolian spot
				Longitudinal pigmented band of nail
				Bowen's disease, pigmented
				Basal cell carcinoma, pigmented
				Ofuji's disease

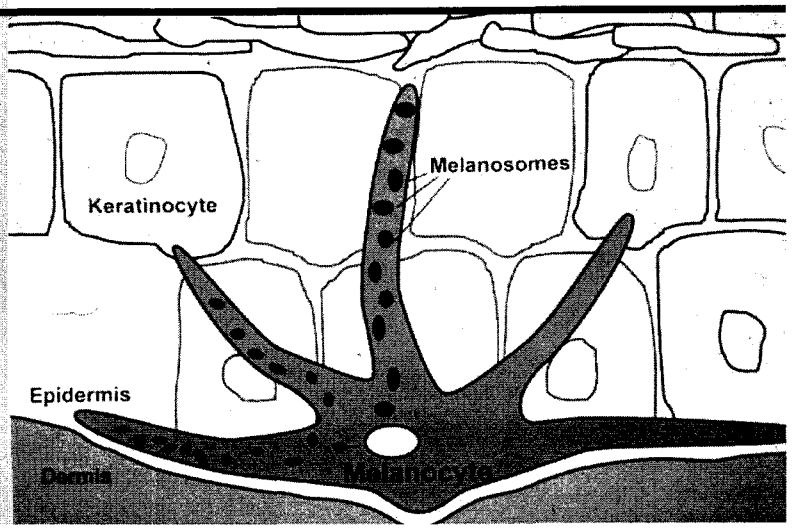
*M. R. Sanchez, unpublished data.
†H. W. Lim, unpublished data. Percentages not available.

(J Am Acad Dermatol 2003;48:143-8.)

Undesired skin pigmentation

- Ultraviolet radiation
- Hyperpigmentation
- Skin Aging

Melanocytes



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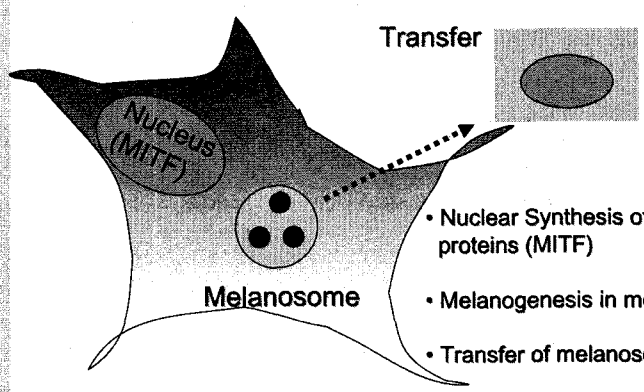
Events in Pigmentation



- Nuclear Synthesis of melanogenic proteins (MITF)
- Melanogenesis in melanosomes
- Transfer of melanosomes

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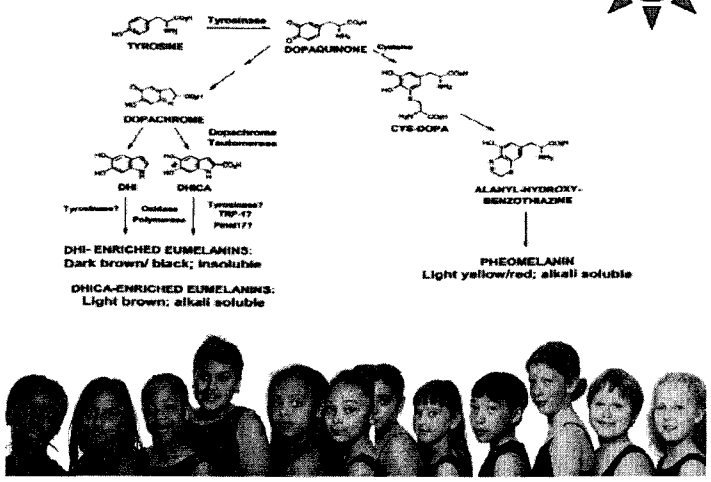
Melanin Type

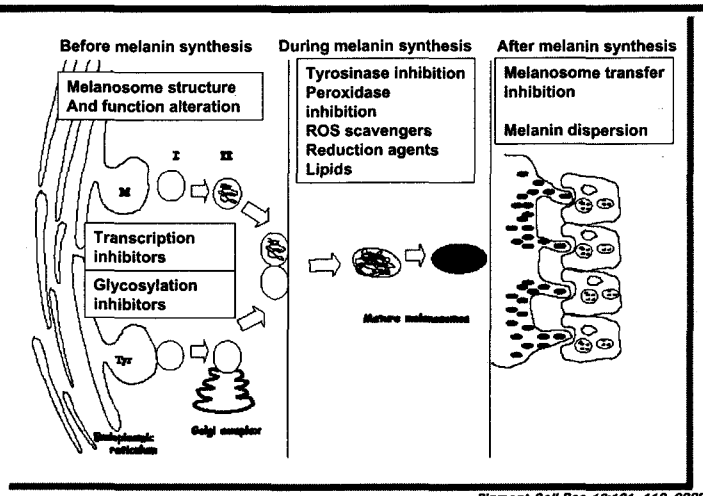


Racial Difference

Comparison of Epidermal Melanocyte Number among Human Racial Groups in Two Different Regions of the Body

RACE	THIGH AND HIP	FOREARM
European American	1000 ± 70* (35)+	1100 ± 80 (9)
Asian	1290 ± 45 (3)	2650 ± 275 (3)
American Indian	1695 ± 115 (6)	2515 ± 250 (6)
African American	1415 ± 255 (7)	1955 ± 150 (4)

Possible target of depigmentation



Pigment Cell Res 16:101-110, 2003

Before melanin synthesis	
Tyrosinase transcription	
C_2-ceramide	Tretinoin
Tyrosinase glycosylation	
$PaSSO_3Ca$	
During melanin synthesis	
Tyrosinase inhibition	
Hydroquinone	Kojic acid
4-hydroxy-anisole	Methyl Gentisate
4-S-CAP & derivatives	Ellagic Acid
Arbutin	Resveratrol
Aloesin	Oxyresveratrol
Azelaic acid	
Peroxidase inhibition	
Methimazole	Phenols/catechols
Product reduction and ROS scavengers	
Ascorbic acid	α-Toc
Ascorbic Acid Palmitate	D, L-α TF
VC-PMG	Hydrocumarins
Thioctic acid	
After melanin synthesis	
Tyrosinase degradation	
Linoleic acid	α-Linolenic acid
Inhibition of melanosome transfer	
Serine protease inhibitors	Niacinamide
Lecthins and Neoglycoproteins	RW-50353
Soybean/milk extracts	
Skin turnover acceleration	
Lactic acid	Retinoic acid
Glycolic acid	Linoleic acid
Liquiritin	

Pigment Cell Res 16:101-110, 2003

Combination therapy

Table 2. Bleaching Formulas

Name of formula	*Active ingredients*
Kligman's formula	Hydroquinone 5% Tretinoin 0.05–0.1% Dexamethasone or betamethasone valearate 0.1% In Hydro-alcoholic base cream or ointment base
Pathak's formula	2% HQ Tretinoin 0.05–0.1% In Hydro-alcoholic base cream or ointment base
Westhorf's formula	N-acetylcysteine 3% HQ 2% Hydrocortisone 1% In Ointment base

Cosmetic Ingredients

Notified whitening agent	
Ingredients	%
Broussonetia extract	2.0%
Arbutin	2.0%
Oil soluble Licolice Extract	0.05%
3-Ethoxy Ascorbic alcd	2.0%

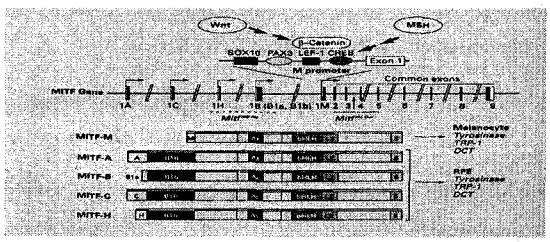
Recent trends

- Nuclear synthesis of melanogenic protein : Mitf regulation/c-kit antagonist
- Melanogenesis
  : Tyrosinase inhibitor/Tyrosinase modification / melanin type
- Melanosome transfer inhibition
  : Transfer/transport inhibitor

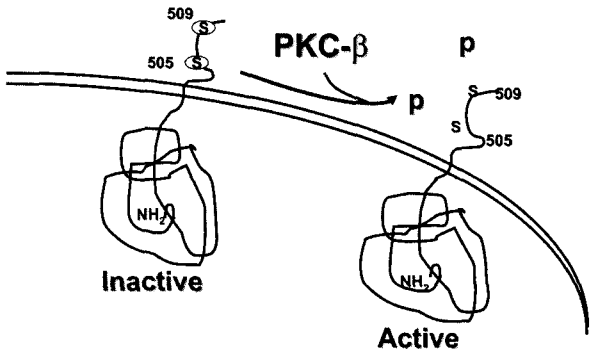
MITF

(Microphthalmia-associated transcriptio factor)

- Master gene for melanocyte development and survival Melanogenesis
- Defect in this gene may result in albanism
- Regulates major antiapoptotic protein BCL2



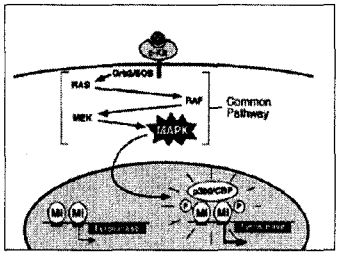
Phosphorylation by PKC- β Leads to the Activation of Tyrosinase



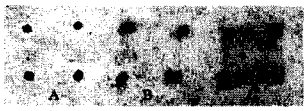
(Park et al, 1999 *J. Biol. Chem.* 274:16470-16478)

c-KIT Receptor

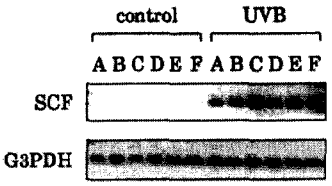
- Cell surface tyrosine kinase receptor
  Important for migration, colonization, proliferation and survival of melanocytes
- Ligand: Stem cell factor (Steel)
- C-kit/Stem cell factor: Melanocyte survival and pigmentation
- Marker for stem-cell melanocytes?



c-kit/SCF affects UVB-induced skin pigmentation



Guinea pig skin

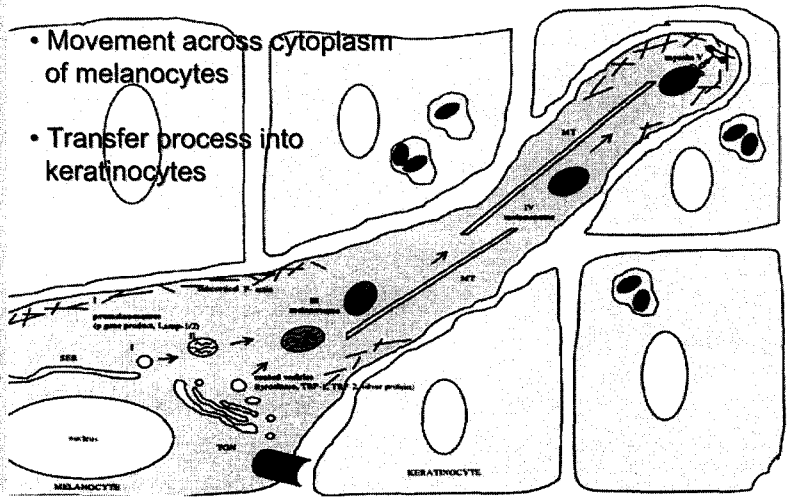


Human epidermis

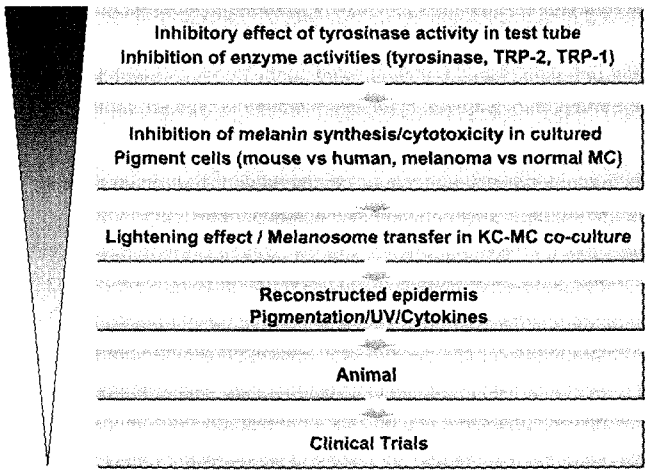
J Invest Dermatol 116:578-586, 2001

Melanosome Transfer

- Movement across cytoplasm of melanocytes
- Transfer process into keratinocytes



Evaluation methods of inhibitory effect of skin lightening agents



Prospects

- Melanocyte Biology
- Melanogenesis
- Pathogenitic mechanism

- Assay system

- More Specific Target
  - Melanosome transport/transfer
  - Tyrosinase structure
  - c-kit regulator
  - Unknown
- Advanced Assay system
  - Co-culture
  - 3D culture
  - Target specific assay system

⇩

Improved Depigmenting agent