CLINICAL INSIGHTS
SPONSORED BY SKINMEDICA®
2016, No. 9

Correcting Uneven Skin Pigmentation: The Complex Biology of Human Skin Color



Kuniko Kadoya, PhD
SkinMedica®, an Allergan Company
Tsing Cheng, PhD
SkinMedica®, an Allergan Company
Rahul C. Mehta, PhD
SkinMedica®, an Allergan Company

Skin conditions related to hyperpigmentation contribute to psychosocial anxiety leading to poor quality-of-life measures.[1,2] Correction of pigmentary conditions remains one of the most sought after goals of aesthetic treatments worldwide. Various forms of melanin are responsible for human skin color.[3] Melanin is synthesized by melanocytes at the base of the epidermis and transported to keratinocytes via a series of complex steps. More than 375 different genes are involved in pigmentation processes, and research is underway to understand their role.[4] In order to create a product to address the multitude of hyperpigmentation issues, it is important to understand the genetics, biology and chemistry of melanin production and distribution. This would allow for a scientifically sound combination of ingredients for correcting a wide range of hyperpigmentary conditions.

PATHWAYS OF MELANOGENESIS AND MELANIN DISTRIBUTION

Melanogenesis comprises multiple pathways and steps. Internal and environmental factors can activate melanocytes via key molecules and receptors (such as α-melanocyte stimulating hormone (αMSH) and melanocortin 1 receptor (MC1R)), leading to up-regulation of microphthalmia transcription factor (MITF). MITF controls the expression of tyrosinase (TYR), tyrosinase-related protein 1 (TYRP1) and DOPAchrome tautomerase (DCT/TYRP2) which are key enzymes in melanin synthesis.[5] TYR, TYRP1 and DCT/TYRP2 are delivered to the melanosomes; these are endosome-derived vesicles where melanin is synthesized, stored and transported.[6] Subsequently, mature melanosomes, packed with melanin, are transferred from the melanocyte to surrounding keratinocytes. Each melanocyte forms an epidermal melanin unit by connecting with about 36 actively regenerating keratinocytes in the basal and supra-basal layers.[7] The melanosomes translocate to melanocyte dendrites, followed by transfer to keratinocytes via multiple proposed mechanisms. Dark skin contains large individual melanosomes with dark eumelanin distributed throughout the cytosol. Light skin contains smaller melanosomes in clusters with light melanin predominantly accumulating as a cap over the nucleus.[3] During the terminal differentiation process pigmented keratinocytes are transformed into corneocytes. As the corneocytes gradually slough off the skin surface, so will the melanin within those cells. Increasing desquamation of skin cells can stimulate keratinocyte turnover and removal of existing melanin.

A COMPREHENSIVE PRODUCT TO TACKLE COMPLEX BIOLOGY

In order to develop a comprehensive product that works on multiple types of pigmentary conditions in people of various ethnic origins, we must utilize our knowledge of the complex biology of melanogenesis. TYR inhibition is one of the key intervention points of any successful pigmentation product; however, the other pathways in melanogenesis also need to be addressed in order to achieve maximum efficacy and outcome. SkinMedica® developed LYT2 with a novel combination of ingredients that modulate many of the key pathways (Table 1).

MELANIN SUPPRESSION IN HUMAN TISSUE MODEL

We performed an in vitro study using a human tissue model consisting of normal human-derived epidermal keratinocytes and melanocytes. The average melanin suppression by LYT2 in seven independent experiments was 45.0±7.65%. We also compared melanin suppression by LYT2 to other hydroquinone-free and retinol-free commercial products. The results show that the comprehensive approach of LYT2 leads to

TABLE 1: THE KEY INGREDIENTS IN LYT2 TARGET MULTIPLE PATHWAYS IN MELANOGENESIS					
	Melanocyte Activation	Melanosome Development	Melanin Production	Melanin Distribution	Melanin Removal
Tranexamic Acid	x			x	
Tetrapeptide-30	x			x	
Vitis Vinifera	x				
Plankton Extracts	x	x	x	x	x
Hydroxyacetaphenone	x				
Niacinamide	x			x	
Phenylethyl Resorcinol			x		
Artemisia Capillaris				x	
Exopolysaccharides					x
Phytic Acid	x		x		x

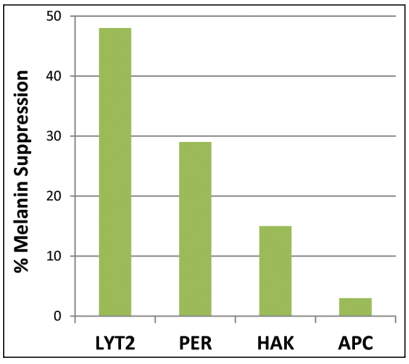

Figure 1: Reduction in melanin level at Day 14 after treatment with LYT2 and commercial products (PER, HAK, APC)

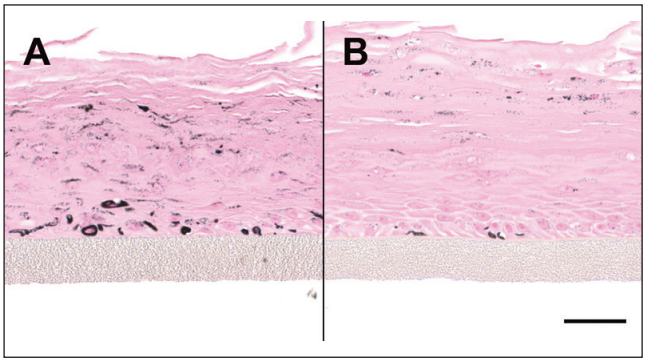

Figure 2: Fontana Masson staining of (A) negative control and (B) LYT2 treated tissue at Day 14. (Scale bar: 50 µm)

greater melanin reduction than partial suppression by products designed to manipulate a few, but not all, critical pigmentation pathways (Figure 1). Histological observation showed great reduction of melanin accumulation in melanocytes and keratinocytes with LYT2, compared to negative control. No cytotoxicity was observed with LYT2 indicating that melanin reduction is in fact due to suppression of melanocyte activity and decreased dendrite formation and not due to melanocytolysis (Figure 2). Hydroquinone, one of the most commonly used prescription treatments for hyperpigmentation, decreases melanin partly due to its melanocytolytic action.[8]

SUPPRESSION OF KEY GENES IN MELANOGENESIS PATHWAYS

The effect of LYT2 on the expression of four key genes for melanogenesis was analyzed by qPCR. LYT2 resulted in significant down-regulation in expression of TYRP1 (58%), MITF (54%), TYR (53%) and DCT/TYRP2 (35%), as compared to negative control. The results strongly indicate that LYT2 regulates multiple genes in melanogenesis affecting multiple biological pathways.

CONCLUSIONS

Thorough understanding of the complex biology of melanogenesis is required to develop a comprehensive product that works on multiple types of pigmentary conditions in people of various ethnic origins. TYR inhibition is one of the key mechanisms utilized by most pigmentation products; however, it alone is not sufficient to provide maximal pigmentation control. We have successfully combined the management of key pathways related to melanogenesis: melanocyte activation, melanosome development, melanin production, melanin distribution, and melanin removal, to create a comprehensive hydroquinone-free and retinol-free product. The outcome clearly shows greater pigmentation control compared to other hydroquinone-free products in skin tissue. ■

1. Balkrishnan R, McMichael AJ, Hu JY. Correlates of health-related quality of life in women with severe facial blemishes. Intl J Dermatol 2006; 45(2):111-115.
2. Levy LL, Emer JJ. Emotional benefit of cosmetic camouflage in the treatment of facial skin conditions: personal experience and review. Clinical, Cosmetic and Investigational Dermatology. 2012;5:173-182.
3. Barsh GS. What Controls Variation in Human Skin Color? PLoS Biology. 2003;1(1):19-22.
4. Yin L, Coelho SG, Valencia JC, et al. Identification of Genes Expressed in Hyperpigmented Skin using Meta-Analysis of Microarray Datasets. The Journal of investigative dermatology. 2015;135(10):2455-2463.
5. Yamaguchi, Y.; Brenner, M.; Hearing, V.J. The regulation of skin pigmentation. J. Biol. Chem. 2007, 282, 27557–27561.
6. Sitaram, A.; Marks, M.S. Mechanisms of protein delivery to melanosomes in pigment cells. Physiology 2012, 27, 85–99.
7. Weiner L, Fu W, Chirico WJ, et al. Skin as a living coloring book: How epithelial cells create patters of pigmentation. Pigment cell & melanoma research. 2014;27(6):1014-1031.
8. Abramowitz J, Chavin W. Acute effects of two melanocytolytic agents, hydroquinone and beta-mercaptoethanolamine, upon tyrosinase activity and cyclic nucleotide levels in murine melanomas. Chem Biol Interact. 1980 Oct;32(1-2):195-208.