Dermatology 2008;217:149
DOI: 10.1159/000135709

Ultraviolet Light Exerts a Major Part of Its Therapeutic Efficacy against Vitiligo by Production of Prostaglandin E₂

M.R. Namazi

Dermatology Department, Shiraz University of Medical Sciences, Shiraz, Iran

Key Words

Vitiligo • Prostaglandin E₂ • Ultraviolet light

Narrow-band ultraviolet (UV) B phototherapy is the UV modality of choice for the treatment of vitiligo. The effect is twofold:

(1) Immunosuppression to stop melanocyte destruction which is suggested to occur by induction of T regulatory (suppressor) cell activity by UVB-induced IL-10 overproduction [1].

(2) To restore pigmentation by increasing the numbers of melanocytes. UV radiation stimulates melanocyte numbers in residual places, e.g. hair follicles and borders of lesional skin. The increase in melanocytes is suggested to be due to a UV-mediated increase in basic fibroblast growth factor and endothelin, which are lower in lesional skin compared to perilesional, nonlesional and healthy skin [1, 2]. UV light may also activate the melanocyte stem cell population resident in the hair follicle and possibly also in the interfollicular epidermis. Melanocyte stem cells would escape any antimelanocyte immune response as they do not express melanocyte differentiation markers [1, 3] and do not express the master regulator of the melanocyte lineage, the microphthalmia-associated transcription factor (MITF). MITF expression is required for melanocyte/melanoma proliferation [1]. UV irradiation activates the p38 stress-activated kinase that not only activates the MITF promoter, but also regulates MITF protein [1].

Below, a hitherto unexplained novel mechanism for the anti-vitiligo effect of UV light is suggested: UV radiation is a potent inducer of cyclooxygenase 2 enzyme and produces high levels of prostaglandin E₂ (PGE₂) in the skin [4]. PGE₂ increases intracellular cAMP levels [5] which stimulate melanogenesis by different ways:

(1) cAMP increases melanosomal pH [6]; increase in melanosomal pH stimulates melanogenesis [6].

(2) cAMP, through activation of protein kinase A, increases the expression of MITF, which in turn stimulates tyrosinase gene expression [7] and, more importantly, induces the proliferation of melanocytic stem cells [1].

(3) cAMP inhibits phosphatidylinositol 3-kinase, whose inhibition stimulates melanogenesis [7].

(4) Glycogen synthase kinase 3β is also activated by cAMP; it regulates neither MITF promoter activity nor the intrinsic transcriptional activity of MITF but by phosphorylation of MITF and increasing its ability to bind the tyrosinase promoter synergizes with it to activate the tyrosinase promoter [7].

Besides stimulating melanogenesis and melanocytic stem cell proliferation, cAMP enhances the activity of glucose-6-phosphate dehydrogenase [4], an important antioxidant enzyme whose levels are decreased in vitiligo [8].

Notably, PGE₂ has an important immunoregulatory function as well. It exerts a suppressive effect on macrophage functions such as antigen presentation and MHC class II expression, decreases the proliferation of Th1 cells and expression or synthesis of IL-1 and TNF-α and increases the production of IL-4, which counterregulates the effects of the type 1 cytokines [5] that are believed to be the dominant cytokines involved in vitiligo [1].

Therefore, production of PGE₂ by UV light could be regarded as a major mode of action of this therapeutic modality against vitiligo.

References

- 1 Westerhof W, d'Ischia M: Vitiligo puzzle: the pieces fall in place. *Pigment Cell Res* 2007;20:345–359.
- 2 Moretti S, Spallanzani A, Amato L, Hautmann G, Gallerani I, Fabiani M, et al: New insights into the pathogenesis of vitiligo: imbalance of epidermal cytokines at sites of lesions. *Pigment Cell Res* 2002;15:87–92.
- 3 Osawa M, Egawa G, Mak SS, Moriyama M, Freter R, Yonetani S, et al: Molecular characterization of melanocyte stem cells in their niche. *Development* 2005;132:5589–5599.
- 4 Namazi MR: UV light may induce hypertrichosis through production of PGE₂. *Med Hypotheses* 2007;68:917–918.
- 5 Namazi MR: The beneficial and detrimental effects of linoleic acid on autoimmune disorders. *Autoimmunity* 2004;37:73–75.
- 6 Ancas A, Thody AJ: Activation of melanogenesis by vacuolar type H⁺-ATPase inhibitors in amelanotic, tyrosinase positive human and mouse melanoma cells. *FEBS Lett* 2000;478:57–60.
- 7 Khaled M, Larribere L, Bille K, Aberdam E, Ortonne JP, Ballotti R, et al: Glycogen synthase kinase 3β is activated by cAMP and plays an active role in the regulation of melanogenesis. *J Biol Chem* 2002;277:33690–33697.
- 8 Agarwal D, Shajil EM, Marfatia YS, Begum R: Study on the antioxidant status of vitiligo patients of different age groups in Baroda. *Pigment Cell Res* 2004;17:289–294.

Dr. M.R. Namazi

Dermatology Department, Faghihi Hospital
Shiraz University of Medical Sciences
Shiraz (Iran)

Tel./Fax +98 711 230 0049, E-Mail namazi_mr@yahoo.com