Research Article

Expression of Tyrosinase, Tyrp1 and Tyrp2 in vitiligo

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Abstract
Vitiligo, an acquired idiopathic pigmentary disorder of skin and hair, is characterized by well-circumscribed asymptomatic white cutaneous macules and patches, where selective destruction of functioning melanocytes. Tyrosinase (TYR) gene family, a major determinant of human pigmentary differences, consists of three members of genes, which produce three proteins called tyrosinase related proteins (Tyrps).
Keywords: Vitiligo, (TYR) gene family, tyrosinase related proteins (Tyrps).

Introduction
Tyrosinase gene family, a major determinant of human pigmentary system, consists of three members of genes, which produce three proteins called Tyrps as follows (Sturm et al., 2001);

- Tyrosinase gene (TYR) produces Tyr protein (Giebel et al., 1991; Ponnazhagan et al., 1994).
- Tyrosinase related protein 1 gene (TYRP1) produces Tyrp1 (Box et al., 1998).
- Tyrosinase related protein 2 gene (TYRP2) produces Tyrp2 (Sturm et al., 2001).

Tyrosinase and Tyrp1 exhibit similar oxidase activities, but the homologous Tyrp2 has a different catalytic capability (Lerner et al., 1950).

Material and Method
The present study included 30 patients with vitiligo vulgaris. They were selected from the Dermatology Out-patient Clinic of Minia University Hospital.

Vitiligo patients were classified into 2 groups as follows;

- **Group 1:** 12 untreated vitiligo patients.
- **Group 2:** 18 vitilgo patients treated by NB-UVB phototherapy.

The study included 5 healthy volunteers as controls.

All patients were subjected to the following;

- Full history taking.
- General clinical and dermatological examination.
- Diagnosis was made by dermatological examination and wood's light
- Taking skin biopsies and analyzed by immunohistochemical staining.

Expression of Tyr, Tyrp1 and Tyrp2 in epidermal cells was evaluated by detection of number of positively stained cells by three independent dermatologists in 1mm length of stained tissue. This number was multiplied by the intensity of staining, which ranged from faint- brown (score1) to deep-brown (score3), and the median value for each case was recorded for further statistical evaluation.

Results
The number of the patients in this study was 30 patients, divided into two groups: 12 untreated vitiligo patients and 18 NB-UVB treated vitiligo patients. The study also included 5 control healthy volunteers.

Immunohistochemical staining of the biopsies obtained from untreated vitiliginous skin (group 1) revealed a significant decrease in Tyrps, however, skin lesions treated by NB-UVB (group 2) revealed increase in the expression of Tyr, Tyrp1 and Tyrp2 enzymes. This increase is statistically significant in Tyrp1 but statistically insignificant in Tyr and tyrp2 when compared to untreated vitiligo lesions (group 1).

In NB-UVB treated patients of group 2, a significant positive correlation was detected between Tyr and Tyrp2 levels.

Discussion
In this study, the depigmented lesions in untreated vitiligo patients of group1 revealed significant low level of Tyr, Tyrp1 and Tyrp2

enzymes, when compared to the normal control values. This result may provide a possible mechanism for vitiligo disease suggesting that depigmentation in vitiligo disease might be related to decreased expression of Tyrps, and consequently inhibition of melanogenesis occurs. Sturm et al., (1998) reported that Tyr activity being 10 times less in white skin people as compared to black skin. Moreover, Yu and Kim (2010) showed that reducuction of melanin contents and Tyr activity was associated with attenuated amounts of Tyr and Tyrp1 protein levels.

Husain et al., (1982) showed that vitiligo skin of human beings contains Tyr which is about 4 to 37% of the corresponding normal skin. Also, Merimsky et al., (1996) reported that anti-Tyr antibodies are found in the sera of patients with diffuse vitiligo. Okamoto et al., (1998) demonstrated that patients with malignant melanoma, vitiligo, and active-specific immunotherapy-induced depigmentation had significant anti-Tyrp 2 IgG titers. The highest level of anti-Tyrp 2 IgG response was found in vitiligo patients.

The immunoprecipitation study of Romero et al., (1994) in normal human MCs showed that Tyr activity and Tyrp1 enzymes revealed a significant increase after UVB treatment but, adramatic decreased of Tyrp 2 enzyme expression was reported.

Conclusion

This study demonstrated that the three studied proteins (Tyr, Tyrp1 and Tyrp2) were decreased to share the same changes in the vitiligo disease. Moreover, these three proteins increased with statistically significance in Tyrp1 and statistically insignificance in Tyr and Tyrp2 upon treatment with NB-UVB. Accordingly, the mechanism of depigmentation in vitiligo disease and repigmentation by NB-UVB treatment are correlated to changes in the expression of these proteins, providing a new insight into the mechanisms of NB-UVB action in treatment of vitiligo disease.

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References

1. Box NF, Wyeth JR, Mayne CJ, O'Gorman LE, Martin NG and Sturm RA (1998): Complete sequence and polymorphism study of the human TYRP1 gene encoding tyrosinase related protein 1. Mamm Genome; 9(1): 50–53.
2. Giebel LB, Strunk KM and Spritz RA (1991): Organization and nucleotide sequences of the human tyrosinase gene and a truncated tyrosinase related segment. Genomics; 9(3): 435–445.
3. Husain I, Vijayan E, Ramaiah A, Pasricha S and Madan NC(1982): Demonstration of tyrosinase in the vitiligo skin of human beings by a sensitive fluorometric method as well as by 14C(U)-L-tyrosine incorporation into melanin. J Invest Dermatol; 78:243-252.
4. Lerner AB, Fitzpatrick TB, Calkins E, SummersonWH(1950): Mammalian tyrosinase. the relationship of copper to enzymatic activity. J Biol Chem;187(2): 793–802.
5. Merimsky O, Shoenfeld Y, Baharav E, Zigelman R, Fishman P(1996):Reactivity to tyrosinase: expression in cancer (melanoma) and autoimmunity (vitiligo). Hum Antibodies Hybridomas; 7 (4): 151-6.
6. Okamoto T, Irie RF, Fujii S, Huang SKS, Nizze AJ, Morton DL and Hoon DSB (1998): Anti-tyrosinase-related protein-2 immune response in vitiligo patients and melanoma patients receiving active-specific immunotherapy. J Invest Dermatol; 111(6):1034–1039.
7. Ponnazhagan S, Hou L and Kwon BS (1994): Structural organization of the human tyrosinase gene and sequence analysis and characterization of its promoter region. J Invest Dermatol; 102(5): 744–748.
8. Roméro C, Aberdam E, Larnier C and Ortonne JP (1994):Retinoic acid as modulator of UVB-induced melanocyte differentiation. Involvement of the melanogenic enzymes expression. J Cell Sci; 107(4):1095-1103.
9. Sturm RA, Box NF and Ramsay M (1998): Human pigmentation genetics: the difference is only skin deep. Bioessays; 20(9): 712–721.

10. Sturm RA, Teasdale RD and Box NF (2001): Human pigmentation genes: Identification, structure and consequences of polymorphic variation. Gene; 277 (1-2): 49-62.

11. Yu JS and Kim K (2010): Effect of combination of taurine and azelaic on antimelanogenesis in murine melanoma cells. J Biomed Sci; 17(suppl 1):S45.