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Current insight into the roles of microRNA 25-5p and microphthalmia-associated transcription factor in the pathogenesis of non-segmental vitiligo

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ABSTRACT

Vitiligo is a common acquired, chronic dermatological disease with loss of functioning melanocytes, affecting skin, hair, mucosa, or all. Non-segmental vitiligo (NSV) is the most common form of vitiligo Melanocyte destruction under oxidative stress may be promoted by microRNA-25-5p (miR-25-5p), which inhibits keratinocytes' production and release of growth factors stem cell factor (SCF) and basic fibroblast growth factor (bFGF). Microphthalmia-associated transcription factor (MITF) is a primary regulator of the function and survival of melanocytes. 48 NSV sufferers and 48 healthy control participants were enrolled in this study. Peripheral blood samples were taken from each subject to measure the messenger RNA (mRNA) expression levels of MITF and miR-25-5p. This was done by using the real-time reverse transcriptase polymerase chain reaction (RT-PCR). The current study investigated the expression profiles of miR-25-5p and MITF in NSV patients compared to healthy controls. The results indicated that NSV patients exhibited a significant upregulation of miR-25-5p expression compared to the control group. Conversely, MITF expression levels were obviously lower in the NSV cohort. Furthermore, analysis within the NSV patient group revealed a negative correlation between miR-25-5p and MITF expression levels, suggesting an inverse relationship. Additionally, miR-25-5p expression displayed a positive correlation with disease activity as measured by the Vitiligo Disease Activity (VIDA) score. Conversely, MITF expression exhibited a negative correlation with VIDA score. Interestingly, no significant correlation was observed between gene expression and the Vitiligo Area Scoring Index (VASI) score, a marker of disease severity. It was concluded from the results that MITF and miR-25-5p are involved in the pathogenesis of NSV.

Keywords: Vitiligo, MicroRNA-25-5p, Microphthalmia-associated transcription factor, Vitiligo Index of Disease Activity Score.

INTRODUCTION

Vitiligo is a multifactorial disease distinguished by a lack of pigmentation resulting from the death or inactivity of melanocytes in the skin, mucosa, or other organs. Genetic, environmental, metabolic, and autoimmune factors are among the etiological possibilities that could play a role in the disease's etiology (Bergqvist *et al.,* 2021). The oxidative stress theory proposes that reactive oxygen species (ROS) are dramatically produced in vitiliginous skin due to an unbalanced redox state, which destroys melanocytes and results in depigmented macules (Bergqvist *et al*., 2020). IL-6, IL-1, TNF-α, and other cytokines cause the melanocytes in vitiligo to overproduce ROS (Thannickal *et al*., 2000).

The response to unfolded proteins (UPr) is a phenomenon that arises from the accumulation of faulty proteins in the endoplasmic reticulum due to oxidative stress (OS). This process aids in the generation of proinflammatory interleukins (IL6 and IL8) and autophagy. The OS-induced upregulation of TRPM2 (transient receptor potential cation channel subfamily M member 2) facilitates the entry of calcium into the melanocyte, ultimately leading to its death (Kang *et al*., 2018). The release of damage-associated molecular patterns, or DAMPs, is enhanced by the OS. These molecules, primarily heat shock protein 70 (HSP70), trigger the innate response by stimulating dendritic cells (DC) and encouraging the involvement of natural killer (NK) cells (Marchioro *et al*., 2022). All of these factors cause ROS to build up in melanocytes, which ultimately causes melanocyte damage and the generation of autoantigens via autophagy, endoplasmic reticulum stress, or apoptosis (Boniface *et al*., 2018).

MicroRNAs (miRNAs) are short, non-coding RNAs that have about 22 nucleotides and control post-transcriptional patterns of gene expression. The pathogenic process of vitiligo involves miRNAs in multiple essential aspects, including the immune response and melanocyte proliferation, differentiation, and apoptosis (Yao *et al*., 2018). In vitiligo, the increase of miR-25-5p due to oxidative stress accelerates melanocyte destruction. Oxidative stress raised the expression of miR-25-5P in keratinocytes and melanocytes, potentially by encouraging the demethylation of the gene that codes for miR-25-5P.

MITF controls the development, pigmentation, proliferation, and cell survival of melanocytes (Liu& Fisherl, 2010). The destruction and malfunction of melanocytes produced by miR-25-5p can be explained by MITF (Al Robaee *et al*., 2022).

The aim of this study was **to** evaluate the possible role and relationship of miR-25-5p and its related gene, MITF, in the pathogenesis of vitiligo.

PATIENTS AND METHODS

This study was carried out at the Department of Dermatology at Menoufia University. The study protocol was approved by the Institutional Medical Ethics Committee, adhering to the ethical principles outlined in the Declaration of Helsinki. The patients were selected all over a period of one year from June 2022 to August 2023. Written informed consent was obtained from all participants. This study enrolled a total of 48 patients diagnosed with NSV and 48 healthy controls.

Inclusion criteria: Patients in the current study could be of any age or sex, and they had a clinical diagnosis of NSV (VIDA 0 or more).

Exclusion criteria: To minimize potential confounding factors, participants were excluded if they had received phototherapy, topical medications (corticosteroids, vitamin D analogs, tacrolimus), or systemic therapies (glucocorticoids, immunosuppressants, biologics) within the past three months before sample collection. Additionally, participants with a history of coagulation disorders, autoimmune diseases (acquired), congenital anomalies or immune-related conditions were excluded from the study.

A comprehensive dermatological examination was performed for each patient, documenting the distribution, severity, and clinical type of vitiligo. The Vitiligo Disease Activity (VIDA) score (Nj00 *et al*., 1999) and Vitiligo Area Scoring Index (VASI) score (Hamzavi *et al*., 2004) were determined for all NSV patients.

Laboratory investigations:

All participants did the following: complete blood count, thyroid function tests,

antithyroid antibodies, erythrocyte sedimentation rate, antinuclear antibody, and rheumatoid factor.

Sample collection and extraction of microRNA:

To separate peripheral blood mononuclear cells (PBMCs), each participant gave 5 ml of venous blood. RNA was isolated from PBMCs using the ABT Total RNA Mini Extraction Kit (Applied Biotechnology, Egypt) in compliance with the manufacturer's instructions. A 2% agarose gel electrophoresis was used to evaluate the total RNA's integrity. RNA samples were then stored at -80°C. Next, following the manufacturer's instructions, cDNA was synthesized using the ABT 2X RT Mix cDNA Synthesis Kit (Applied Biotechnology, Egypt).

Quantitative real-time PCR (qPCR)

Real-time PCR assays were conducted using the 7500 Fast Real-Time PCR System (Applied Biosystems, Foster City, California, USA) and Power SYBR Green PCR Master Mix. The 40 cycles of real-time PCR were performed in triplicate using the following protocol: initial denaturation at 95°C for 5 minutes, annealing at 60°C for 30 seconds, and extension at 72°C for 30 seconds. After that, the control gene GAPDH was used as a reference, and the relative levels (fold changes) of MITF and miR-25-5P expressions were measured using the 2-△△Ct technique. Table (1) contains a list of the primer sequences used in this investigation.

Table 1: The primer sequence for Q-PCR.

Primer	Sense	Antisense	References
GAPDH	GAAATCCCATCACCATCTTCCAGG	TGAGCCCCAGCCTTCTCCAT	Rangel *et al*., 2009
MIR 25-5p	CGGAGACTTGGGCAATT	GAACATGTCTGCGTATCTC	Wang *et al*., 2020
MITF	GCGCAAAAGAACTTGAAAAC	CGTGGATGGAATAAGGGAAA	Inoue *et al*., 2023

Statistical Analysis:

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0**. (**Armonk, NY: IBM Corp.**)** Qualitative data were described using numbers and percent. The Shapiro-Wilk test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). The Significance of the obtained results was judged at the 5% level.

The tests used were

1 - Chi-square test:

For categorical variables, to compare between different groups.

2 - Mann Whitney test: For abnormally distributed quantitative variables, to compare between two studied groups.

3- Spearman coefficient: To correlate between two abnormally distributed quantitative variables.

Key Terms:

- Sensitivity

The capacity of the test to correctly identify diseased individuals in a population "true positives". The greater the sensitivity, the smaller the number of unidentified cases "false negatives"

- Specificity: The capacity of the test to correctly exclude individuals who are free of the disease "true negatives". The greater the specificity, the fewer "false positives" will be included

- Positive Predictive value (PPV): The probability of the disease being present, among those with positive diagnostic test results

– Negative Predictive value (NPV): The probability that the disease was absent,

among those whose diagnostic test results were negative.

RESULTS

Routine laboratory testing, including complete blood count, thyroid function tests, antithyroid antibodies, erythrocyte sedimentation rate, antinuclear antibody, and rheumatoid, yielded normal results. The clinical results for the study groups are displayed in Tables (2 and 3). There was no discernible difference in age (P = 0.256) or sex (P = 0.413) between the study groups.

Table (2). Comparison between the two studied groups according to demographic data

	Cases (n = 48)		Control (n = 48)		Test of Sig.	P
	No.	%	No.	%		
Sex Male Female	 20 28	 41.7 58.3	 24 24	 50.0 50.0	χ^2= 0.671	0.413
Age Min. – Max. Mean ± SD. Median (IQR)	 4.0 – 61.0 17.50(11.5– 35.0) 17.50(11.5– 35.0)		 5.0 – 60.0 27.19 ± 15.94 24.50(18.0– 41.0)		U= 997.0	0.256

Table (3). Distribution of the studied cases according to VIDA score, VASI score and duration (years).

	No.	%
VIDA Score 0 +1 +2 +3 +4	 5 14 13 10 6	 10.4 29.2 27.1 20.8 12.5
VASI Score Min. – Max. Mean ± SD. Median (IQR)	 1.80 – 27.0 12.11 ± 6.74 11.60 (7.2 – 16.5)	
Duration (years) Min. – Max. Mean ± SD. Median (IQR)	 1.0 – 15.0 4.90 ± 3.84 3.0(2.5 – 7.0)	

IQR: Inter quartile range. SD: Standard deviation. χ^2: Chi square test U: Mann Whitney .test
p: p value for comparison between the studied categories *: Statistically significant at p ≤ 0.05

MiRNA-25-5p and MITF gene expression:

(a) Expression of miR-25-5p:

The PBMCs of both research groups showed expression of miR-25-5p. Compared to healthy controls, who had a mean ±SD of 0.69 ± 0.75 (U=322, P<0.001, Fig. 1), patients with NSV had significantly higher relative levels of its expression, with a mean ±SD of 3.67 ± 3.11. The relative levels of miR-25-5p expression in the PBMCs did not significantly correlate with the patients' age or sex. The duration of the disease (r= 0.037, P= 0.804) and its severity (r= 0.168, P= 0.253) as assessed by the VASI score, also showed no significant correlation. The disease activity as determined by the VIDA

score, on the other hand, showed a substantial positive correlation (r = 0.872, P<0.001, Fig. 2).

(b) Expression of MITF:

Every participant's PBMCs showed expression of MITF. In comparison to healthy controls, who had a mean±SD of 1.89±1.23 (U=583 P<0.001, Fig. 1), patients with NSV had statistically significant downregulation of its expression at relative levels, with a mean ±SD of 0.91 ± 0.54. A significant negative correlation was discovered (r= -0.907, P<0.001, Fig. 2) between the disease activity measured by the VIDA score and the relative expression levels of MITF in NSV patients. However, there was no significant correlation found between its expression and the other clinical parameters of the research participants, including age, sex, disease duration (r= -0.172, P = 0.244), or severity as assessed by the VASI score (r= - 0.154, P =0.295).

(c) The relative levels of miR-25-5p and MITF expression were shown to be significantly negatively correlated in NSV patients (r= -0.752, P<0.001, Fig. 3).

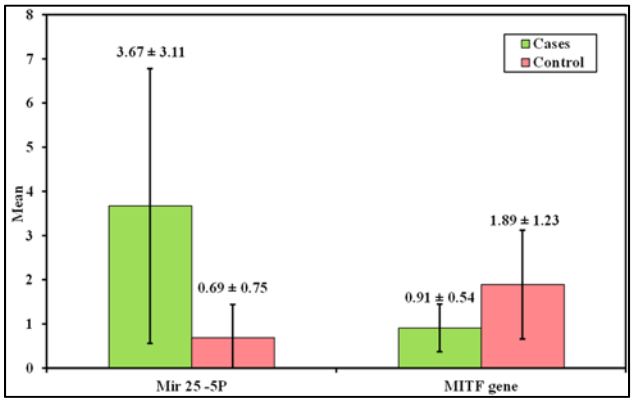

Fig. (1): Comparison between the two studied groups according to Mir 25 -5P and MITF gene

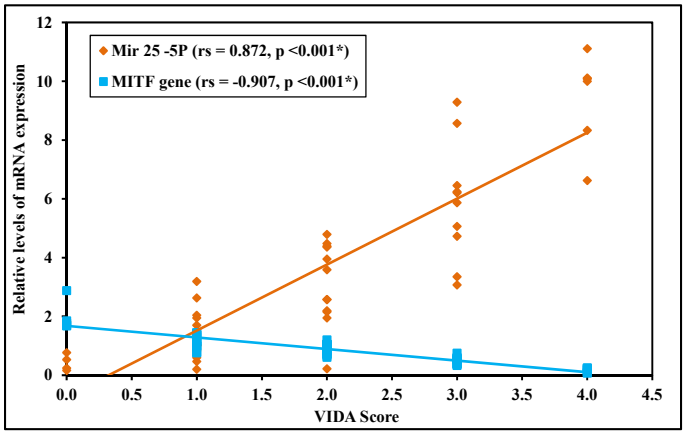

Fig. (2): Correlation between VIDA Score with Mir 25 -5P and MITF gene in cases group

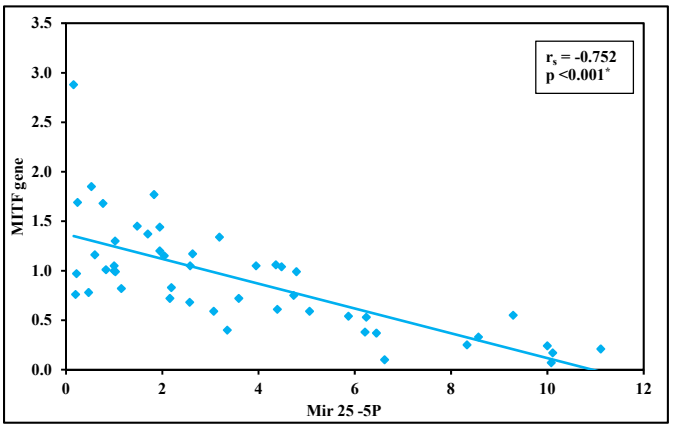

Fig. (3): Correlation between Mir 25-5P with MITF gene in cases group

DISCUSSION

Oxidative stress is one of the main triggers for the development of vitiligo (DiDalmazi *et al*., 2016). According to the oxidative stress theory, there is an increased generation of ROS, which triggers an immunological response and causes melanocyte death. ROS is responsible for only a small percentage of melanocyte deaths. Melanocyte self-tolerance is impaired by the inflammation and antigen exposure caused by these melanocyte deaths. The vast majority of melanocyte deaths in vitiligo are then directly caused by self-responsive immune function (Xuan *et al*., 2022). Deregulated miRNAs may contribute to the development of vitiligo by controlling the expression and activity of genes linked to oxidative stress in melanocytes. A greater number of studies have demonstrated that the expression of miRNAs varies in vitiligo patients' PBMCs and skin lesions. Through controlling the function of melanocytes, miRNAs contribute to the pathophysiology of vitiligo (Zhang *et al*., 2021).

This study revealed a significant upregulation of miR-25-5p expression in PBMCs isolated from NSV patients compared to healthy controls. Interestingly, no statistically significant correlation was observed between miR-25-5p levels and most clinical parameters in NSV patients, with the sole exception of the VIDA score, which displayed a positive correlation. These findings align with previous reports by Shi *et al*. (2013, 2016) and Li (2020). To elucidate these results, we investigated the potential role of oxidative stress in promoting miR-25-5p expression. We observed that oxidative stress induces demethylation of the miR-25 encoding gene, leading to increased miR-25-5p expression in both keratinocytes and melanocytes. Notably, miR-25-5p overexpression inhibited the production and secretion of stem cell factor (SCF) and basic fibroblast growth factor (bFGF) from keratinocytes, potentially compromising melanocyte survival under oxidative stress conditions (Dopytalska *et al*., 2023).

Furthermore, our study demonstrated a significant downregulation of MITF expression in NSV patient PBMCs compared to controls. We also observed a significant negative correlation between relative MITF and miR-25-5p expression levels, as well as a strong negative correlation between MITF expression and VIDA score in NSV patients. These findings are consistent with previous work by Shi *et al*. (2014, 2016). MITF is a key regulator of melanocyte function, controlling the expression of tyrosinase (TYR), tyrosine-related protein-1 (TYRP-1), and dopachrome tautomerase (DCT), the three primary enzymes involved in melanogenesis. Additionally, MITF upregulates the anti-apoptotic factor B-cell

lymphoma 2 (BCL2), and its deletion in melanocytes leads to extensive apoptosis (Gelmi *et al*., 2022). Mechanistically, our study suggests that the elevated miR-25-5p levels directly target the 3'UTR of the MITF gene in melanocytes, significantly inhibiting its protein expression. Moreover, restoration of miR-25-5p reduced cell cycle progression and promoted H2O2-induced melanocyte apoptosis (Vachtenheim & Borovanský, 2010). Furthermore, miR-25-5p has been shown to inhibit tyrosinase activity and the expression of TYR and TYRP1, thereby affecting melanin production and melanosome transport within melanocytes. Collectively, these findings suggest that miR-25-5p overexpression in NSV may play a crucial role in suppressing MITF, which in turn disrupts melanocyte maintenance and function, potentially contributing to the depigmentation process observed in vitiligo (Dopytalska *et al*., 2023).

Shi *et al*. (2016) further demonstrated that miR-25-5p impairs the antioxidant response by blocking the MITF-APE1 pathway, rendering melanocytes more susceptible to oxidative stress-induced damage. APE1, a transcription target of MITF, plays a critical role in the cellular antioxidant response. Additionally, reintroduction of MITF in melanocytes transfected with miR-25-5p mimics increased tyrosinase activity and melanin content, highlighting the protective role of MITF (Shi *et al*., 2016). Taken together, these findings suggest that oxidative stress-mediated miR-25-5p overexpression contributes to melanocyte degeneration via an MITF-dependent pathway, potentially disrupting the paracrine protective function of keratinocytes and ultimately leading to vitiligo development (Yan *et al*., 2020).

CONCLUSION

This research may offer a crucial window into the pathophysiology of NSV. The PBMCs of individuals with vitiligo have shown significant changes in the expressions of both miR-25-5p and MITF. Additionally, our research has revealed significant correlations between the two expressions and the disease activity measured by the VIDA score (positive for miR-25-5p and negative for MITF expressions), indicating that they play a vital role in the development and aggravation of vitiligo through a complex relationship. As a result, we proposed that the relationship between MITF and miR-25-5p could be used as a prospective immunotherapeutic strategy for vitiligo.

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رؤية حالية حول أدوار الميكرو RNA 25-5P وعامل النسخ MITF فى مسببات مرض البهاق غير القطعى

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المستخلص

البهاق هو مرض جلدي مزمن شائع مكتسب يتميز بفقدان الخلايا الصبغية الوظيفية، ويؤثر على الجلد والشعر والأغشية المخاطية، أو جميعها. البهاق غير القطعي (NSV) هو الشكل الأكثر شيوعًا من البهاق، ويتميز بوجود مناطق بيضاء حليبية غير متقشرة ذات حواف واضحة تشمل جانبي الجسم. تهدف الدراسة الحالية إلى العمل لتقييم الدور المحتمل وعلاقة MiRNA 25-5p وMITF في التسبب في البهاق المرضى. تم اجراء الدراسة على عدد48 مريض يعانى من البهاق و48 حالة سليمة وقد تم إجراؤه في عيادة الأمراض الجلدية بقسم الجلدية جامعة المنوفية خلال الفتراة ما بين يونيو 2022 و اغسطس 2023 . أظهرت نتائج الدراسة ان خلايا الدم من كلا مجموعتي البحث ان نسبة مستويات تعبير miR-25-5p لدى المرضى الذين يعانون من NSV كانت أعلى بشكل ملحوظ من تعبيره فى الاصحاء و أظهرت خلايا الدم لكل مشارك من أظهر المرضى الذين يعانون من NSV تعبيرًا عن MITF منخفضا بالمقارنة مع الأفراد الأصحاء ذا دلالة إحصائية في تعبيره عن المستويات النسبية.

وقد امكن الاستنتاج **ان** خلايا الدم من الأفراد المصابين بالبهاق قد أظهرت تغييرات ملحوظة في تعبير كل من miR-25-5p وMITF. علاوة على ذلك، كشفت النتائج عن وجود ارتباطات هامة بين التعبيرين ونشاط المرض المقاس بواسطة درجة VIDA (إيجابي لتعبيرات miR-25-5p وسلبي لتعبيرات MITF)، مما يشير إلى أنهما يلعبان دورًا حيويًا في تطور وتفاقم البهاق من خلال علاقة معقدة.

الكلمات الدالة : البهاق، الميكرو RNA-25-5p، عامل النسخ المرتبط MITF ، مؤشر نشاط مرض البهاق.