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MODERN VIEWS ON THE PATHOGENESIS OF VITILIGO



Mavlyanova Shakhnoza Zakirovna[1], Shukurov Ikhlosjon Boltaevich[1], Yakhshieva Malohat Farmonovna[2]
1 - Republican Specialized Scientific and Practical Medical Center of Dermatovenerology and Cosmetology, Republic of Uzbekistan, Tashkent;
2 - Bukhara State Medical Institute, Republic of Uzbekistan, Bukhara

ВИТИЛИГО ПАТОГЕНЕЗИДА ЗАМОНАВИЙ ҚАРАШЛАР

Мавлянова Шахноза Закировна[1], Шукуров Ихлосжон Болтаевич[1], Яхшиева Малохат Фармоновна[2]
1 – Республика ихтисослаштирилган дерматовенерология ва косметология илмий – амалий тиббиёт маркази, Ўзбекистон Республикаси, Тошкент ш.;
2 - Бухоро давлат тиббиёт институти, Ўзбекистон Республикаси, Бухоро ш.

СОВРЕМЕННЫЕ ВЗГЛЯДЫ НА ПАТОГЕНЕЗ ВИТИЛИГО

Мавлянова Шахноза Закировна[1], Шукуров Ихлосжон Болтаевич[1], Яхшиева Малохат Фармоновна[2]
1 - Республиканский специализированный научно – практический медицинский центр дерматовенерологии и косметологии, Республика Узбекистан, г. Ташкент;
2 - Бухарский государственный медицинский институт, Республика Узбекистан, г. Бухара

e-mail: shahnoza_m@mail.ru

Резюме. *Витилиго – бу дерматологияда энг кенг тарқалган гипомеланоз бўлиб, атрофмуҳит омиллари, метаболик ва оксидланиш стресс, иммунитет тизимнинг фаоллиги ва ҳужайра тузилишидаги анормаллик билан боғлиқ бўлган отоиммун генетик воситачи касаллик сифатида таснифланади. Мақолада витилиго патогенези бўйича замонавий маълумотлар ифодаланган.*

Калит сўзлар: *витилиго, оксидланиш стресс, хотира Т ҳужайралари, туғма иммунитет, адаптив иммунитет, тартибга солувчи Т ҳужайлари.*

Abstract. *Vitiligo is the most common hypomelanosis in dermatology, classified as an autoimmune genetically mediated disease associated with environmental factors, metabolic and oxidative stress, immune system activity and abnormalities in cell structure. The article is a review. The current data on the pathogenesis, of vitiligo are presented.*

Keywords: *vitiligo, oxidative stress, memory T cells, innate immunity, adaptive immunity, regulatory T cells.*

Relevance. Vitiligo is a multifactorial chronic inflammatory skin disease, with a polygenic type of inheritance, is an idiopathic dyschromia of the skin, characterized by the appearance of depigmented, often symmetrically arranged spots of various sizes, milky-white outlines with a surrounding area with moderate hyperpigmentation and a tendency to peripheral growth [2,6,11,15]. Vitiligo is characterized by a chronic, in most cases progressive course, expressed in an increase in the number and the size of the foci. It was found that the appearance of depigmentation foci is caused by the destruction of melanocytes in the affected skin [2,11]. The prevalence of vitiligo, depending on the geographical region, in various ethnic groups is diverse and ranges from 0.5 to 2% of the population as a whole, with young age accounting for up to 70% of cases [8,31]. Men and women suffer equally, although women and girls seek counseling more often, perhaps because of the greater negative social impact [8, 16, 23]. Vitiligo can begin at any age, but it is more often manifested in the age group of 10-30 years. Although vitiligo does not affect life expectancy, the difference in color has a serious impact on the quality of life and mental well-being of patients, as patients are often stigmatized and socially isolated, as well as more susceptible to mental illness [3, 24, 32].

The etiology and pathogenesis of vitiligo are still insufficiently studied. The disease is multifactorial, both exogenous and endogenous factors are important in its development. Exogenous factors include stress, mechanical irritation and trauma (Kebner phenomenon), excessive ultraviolet irradiation and chemical agents. Of the endogenous ones, somatic and in-

fectious diseases (autoimmune thyroiditis, rheumatoid arthritis, lupus erythematosus, liver diseases of infectious or toxic origin, worm infestations), taking medications that affect the pigment-forming function of melanocytes are most often noted [4]. Many mechanisms of destruction of melanocytes in vitiligo have been proposed. These include genetic, autoimmune reactions, oxidative stress, formation of inflammatory mediators and mechanisms of melanocyte detachment. Apparently, both innate and adaptive elements of the immune system are involved [2,5,11,36]. Wednesday. The earliest trigger factors that lead to vitiligo are not fully understood. Numerous studies show that the combination of internal defects of melanocytes and exposure to certain environmental factors may play a central role in the onset of the disease. This was evident in the example of a group of factory workers who developed vitiligo after exposure to monobenzone, an organic chemical phenol. More recent studies have confirmed that exposure to other phenolic and catecholic chemicals found in dyes (especially hair dyes), resins/adhesives, was associated with the occurrence of vitiligo [20,33].

Genetics. Convincing data from numerous studies indicate the importance of genetic factors in the development of vitiligo, although it is obvious that these influences are complex. The risk of developing the disease in a patient's brother or sister is 6%, and for identical twins - 23% [7]. In addition, patients with vitiligo and their relatives have an increased risk of developing other autoimmune diseases, including autoimmune thyroiditis, type 1 diabetes, malignant anemia and Addison's disease. [23]. These early observations were later confirmed by large-scale genome-wide association studies (GWAS), which revealed about 50 different genetic loci that create the risk of vitiligo [10], encoding components of both the innate (NLRP1, IFIH1, CASP7, C1QTNF6, TRIF) and adaptive immune systems (FOXP3, BACH2, CD80, CCR6, PTPN22, IL2R, alpha GZMB, HLA class I and II) [29]. Thus, the NALP1 gene on chromosome 17p13 encoding the leucine-rich repeating protein 1 NACHT is a regulatory.

Oxidative stress. Oxidative stress is a condition of tissues characterized by an increased level of oxygen radicals in them, i.e. reactive oxygen species (ROS), which have a high reactivity and cause, in particular, modification of proteins, carbohydrates, lipids, nucleic acids. ROS play an important role in a number of metabolic processes. Normally, the formation and decay of ROS are in a state of balance, protecting cellular structures from damage and ensuring that they perform important signaling functions. They affect the functional activity of cells due to the metabolism of Ca2+, stimulation of protein phospholation, lipid hydrolysis, activation of transcription factors, participate in the formation of biologically active regulators, provide immune responses [2]. Studies suggest that oxidative stress may be the initial event in the destruction of melanocytes [27, 35]. Indeed, it has been found that the melanocytes of patients with vitiligo are more susceptible to oxidative stress than the melanocytes of healthy people. Evidence suggests that the melanocytes of patients with vitiligo have internal defects that reduce their ability to manage cellular stress. Epidermal cells, including melanocytes, are constantly exposed to environmental stressors such as UV radiation and various chemicals that can increase ROS production. While healthy melanocytes are able to mitigate these stressors, the melanocytes of patients with vitiligo seem to be more vulnerable. High concentrations of epidermal H_2O_2 and reduced levels of catalase, a critical enzyme that protects cells from oxidative damage, were found in the skin of patients with vitiligo [16,30].

There is a widespread change in ant imbalance of elevated markers of oxidative stress (superoxide dismutase, malondialdehyde, ROS) and significant depletion of antioxidant mechanisms (catalase, glutathione peroxidase, glutathione reductase, thioredoxin reductase and thioredoxinase, thioredoxinase, as well as reparative enzymes methionine sulfoxide reductase A and B) in the skin and blood [15, 35]. It has been suggested that this imbalance between pro-oxidants and antioxidants in vitiligo is responsible for the increased sensitivity of melanocytes to external pro-oxidant incentives [16, 27, 35]. Generation and accumulation of ROS, in turn, can cause DNA damage, oxidation and fragmentation of proteins and lipid peroxidation, thereby disrupting their cellular function [11, 16]. Reduced adhesion of melanocytes due to oxidative stress was found at the borders of vitiligo lesions, which may explain the Kebner phenomenon [22, 33]. The interaction of melanocytes and keratinocytes does not require specific adhesive structures, such as desmosomes, but simple adhesive molecules, such as integrins and cadherins. In the skin not affected by the lesion, in patients with vitiligo, the expression of e-cadherins is reduced, and the expression of tenascin, an anti-adhesion molecule, is increased [33]. In the skin of vitiligo, chronic friction can activate epithelial cells, which, in turn, convert mechanical forces into biochemical signals [35], causing intracellular stress and subsequent changes in cadherin expression [22].

ROS are endogenous toxic agents that cause cell death and reduce the function of melanocytes [7]. They are contained in high concentrations in the epidermis, blood serum, tissue fluid of depigmented skin areas in vitiligo, which, together with the insufficiency of the antioxidant system, plays an important role in the development and progression of the disease [1, 2, 44]. Innate immunity. Innate immunity in vitiligo eliminates the gap between oxidative stress and adaptive immunity. It is likely that the activation of innate immunity cells occurs at an early stage of vitiligo due

to the perception of exogenously or endogenously induced stress signals released by melanocytes and possibly keratinocytes [43]. According to studies of genome-wide associations, multiple susceptibility loci associated with genes that control innate immunity are involved in patients with vitiligo [29]. This probably causes a violation of the regulation of innate activation in response to melanocyte stress, which manifests itself in the attraction of innate populations, such as natural killer cells (NK), as well as in the production and release of high levels of pro-inflammatory proteins and cytokines, including heat shock proteins (HSP), IL-1ß, IL-6 and IL-8 [38].

Among the larger HSP molecules, inducible HSP70 (HSP70i) is unique because it can be secreted by chaperone peptides specific to the original host cells, protecting cells from apoptosis [34]. It has recently been shown that HSP70i is important for the pathogenesis of vitiligo in a mouse model due to the induction of inflammatory dendritic cells, which themselves can be cytotoxic or carry and present melanocyte-specific antigens to T cells in lymphoid tissues [36,38]. It has been suggested that this is a key step in the cross-interaction between innate and adaptive immunity, leading to T-cell-mediated autoimmune destruction of melanocytes [35, 37]. Induced heat shock protein 70 (HSP70i), calreticulin (CRT) and high mobility group B1 protein (HMGB1) are the most studied molecules in vitiligo [11, 13].

Conclusion. Vitiligo is a common multifactorial skin disease with a very complex pathogenesis. Although significant progress has been made recently in understanding vitiligo, uncertainty remains as to what ultimately causes the destruction of melanocytes, and further research is needed to fully elucidate the pathogenesis of vitiligo. The identification of biological mediators and molecular mechanisms that lead to metabolic defects and, consequently, to melanocyte degeneration and autoimmunity is important for identifying new therapeutic targets and drugs that can prevent, stop the progression of the disease or even cure vitiligo. The experience of systemic biological therapy targeting cytokines, as in psoriasis, suggests that a similar approach can be successfully used in vitiligo.

Literature:

1. Alikhan A, Felsten LM, Daly M, Petronic Rosic V. Vitiligo: a comprehensive overview Part I. Introduction, epidemiology, quality of life, diagnosis, differential diagnosis, associations, histopathology, etiology, and work-up. J Am Acad Dermatol. 2011 Sep;65(3):473–91.
2. Alkhateeb A, Fain PR, Thody A, Bennett DC, Spritz RA. Epidemiology of vitiligo and associated autoimmune diseases in Caucasian probands and their families. Pigment Cell Res. 2003;16(3):208–214
3. Arifov S.S., Shukurov I.B NO-ergic system in vitiligo Pathology No. 2 2009. pp. 20-23.
4. Arifov S.S., Shukurov I.B. Some aspects of the clinical course of vitiligo according to the Bukhara Regional CVD. Problems of dermatovenerology Ukraine Harkov 2009. pp. 301-302.
5. Arifov S.S., Shukurov I.B. Some medical and social aspects of vitiligo. Ukrainian Journal of Dermatovenerology and Cosmetology No. 1(40) 2011.
6. Bergqvist C, Ezzedine K. Vitiligo: A Review Dermatology. 2020;236(6):571-592. doi: 10.1159/000506103. Epub 2020 Mar 10.
7. Bickers DR, Athar M. Oxidative stress in the pathogenesis of skin disease. J Invest Dermatol. 2006 Dec;126(12):2565–75
8. Boldyrev A.A. Oxidative stress and the brain. Sorovsky Educational magazine. 2001; 4: 21-8
9. Boniface K, et al. Vitiligo: focus on clinical aspects, immunopathogenesis, and therapy. Clin Rev Allergy Immunol. 2018; 54:52–67.
10. Cui T, Zhang W, Li S, et al. Oxidative stress-induced HMGB1 release from melanocytes: a paracrine mechanism underlying the cutaneous inflammation in vitiligo. J Invest Dermatol. 2019;139(10):2174–2184. e.
11. Dwivedi M, et al. Regulatory T cells in vitiligo: implications for pathogenesis and therapeutics. Autoimmun Rev. 2015 Jan;14(1):49–56.
12. Eby JM, et al. CCL22 to Activate Treg Migration and Suppress Depigmentation in Vitiligo. J Invest Dermatol. 2015 Jun;135(6):1574–80
13. Frączek A, Owczarczyk-Saczonek A, Placek W. The role of TRM cells in the pathogenesis of vitiligo-a review of the current state-of-the-art. Int J Mol Sci. 2020; 21:3552.
14. Gill L, et al. Comorbid autoimmune diseases in patients with vitiligo: A cross-sectional study. J Am Acad Dermatol. 2016;74(2):295–302
15. Hamidizadeh N, et al. Evaluating prevalence of depression, anxiety and hopelessness in patients with vitiligo on an Iranian population. Health Qual Life Outcomes. 2020; 18:20.
16. Harris JE, et al. A mouse model of vitiligo with focused epidermal depigmentation requires IFN-gamma for autoreactive CD8(+) T-cell accumulation in the skin. J Invest Dermatol. 2012;132(7):1869–1876
17. Harris JE. Cellular stress and innate inflammation in organ-specific autoimmunity: lessons learned from vitiligo. Immunol Rev. 2016 Jan;269(1):11–25.
18. Ismailov R.G. Etiopathogenetic aspects of vitiligo in modern interpretation // Bulletin of problems of biology and medicine. 2012. pp. 14-17.
19. Jin Y, Birlea SA, Fain PR, Ferrara TM, Ben S, Riccardi SL, et al. Genome-wide association analyses identify 13 new susceptibility loci for generalized vitiligo. Nat Genet. 2012;44(6):676–680
20. Krüger C, Schallreuter KU. A review of the worldwide prevalence of vitiligo in children/ adoles-

cents and adults. Int J Dermatol. 2012 Oct;51(10):1206–12.
21.Kruglova L.S. Vitiligo: modern views on etiology, pathogenesis and methods of therapy. Russian Journal of Skin and Venereal Diseases. 2016; 19(4): 241-244. DOI: 10.18821/1560-9588-2016-19-4-241-244
22.Lai YC, Yew YW, Kennedy C, Schwartz RA. Vitiligo and depression: a systematic review and meta-analysis of observational studies. Br J Dermatol. 2017; 177:708–718.
23.Lin M, Zhang BX, Shen N, Dong XJ, Zhang C, Qi XY, et al. Regulatory T cells from active non-segmental vitiligo exhibit lower suppressive ability on CD8+CLA+ T cells. Eur J Dermatol. 2014 Nov-Dec;24(6):676–82
24.Maresca V, Roccella M, Roccella F, Camera E, Del Porto G, Passi S, et al. Increased sensitivity to peroxidative agents as a possible pathogenic factor of melanocyte damage in vitiligo. J Invest Dermatol. 1997 Sep;109(3):310–3.
25.Mavlyanova Sh. Z., Shukurov I. B., Yahshiyeva M. F. //Assessment of the Dermatological Index of the Symptom Scale in Patients with Seborrheic Dermatitis and Opportunistic Infection Based On the Use of Natural Silicon Oxide //Annals of R.S.C.B., Vol. 25, Issue 4, 2021, Pages. 3922 – 3930 Received 05 March 2021; Accepted 01 April 2021.
26.Mosenson JA, et al. Mutant HSP70 reverses autoimmune depigmentation in vitiligo. Science translational medicine. 2013;5(174):174ra28
27.Picardo M, et al. Vitiligo. Nat Rev Dis Primers. 2015 Jun;1(1):15011
28.Rashighi M, Agarwal P, Richmond JM, Harris TH, Dresser K, Su MW, et al. CXCL10 is critical for the progression and maintenance of depigmentation in a mouse model of vitiligo. Sci Transl Med. 2014 Feb;6(223): 223ra23.
29.Richmond JM, et al. Keratinocyte-Derived Chemokines Orchestrate T-Cell Positioning in the Epidermis during Vitiligo and May Serve as Biomarkers of Disease. J Invest Dermatol. 2017 Feb; 137(2):350–8.
30.Richmond JM, Masterjohn E, Chu R, Tedstone J, Youd ME, Harris JE. CXCR3 Depleting Antibodies Prevent and Reverse Vitiligo in Mice. J Invest Dermatol. 2017 Apr;137(4):982–5.
31.Sabirov U.Yu., Azimova F.V., Toirov B.A., Muminova S.R., Nazarova I.I. The Wnt signaling pathway and its significance in the development of vitiligo. // Medical News Magazine. Minsk, 2019. - No. 12. - S. 22-26. (14.00.00; №82)
32.Shen C, Gao J, Sheng Y, Dou J, Zhou F, Zheng X, et al. Genetic Susceptibility to Vitiligo: GWAS Approaches for Identifying Vitiligo Susceptibility Genes and Loci. Front Genet. 2016; 7:3.
33.Shukurov I.B., Yakhshieva M.F., The study of the prevalence and medical and social aspects of vitiligo in the Bukhara region Universum: medicine and pharmacology.Moscow 2021.P. 8-13.
34.Singh RK, et al. The role of IL-17 in vitiligo: a review. Autoimmun Rev. 2016; 15:397–404
35.Speeckaert R, et al. Critical appraisal of the oxidative stress pathway in vitiligo: a systematic review and meta-analysis. J Eur Acad Dermatol Venereol. 2018 Jul; 32(7):1089–98
36.Spritz R.A. Six decades of vitiligo genetics: genome-wide studies provide insights into autoimmune pathogenesis. J Invest Dermatol. 2012;132(2):268–273.
37.Toosi S, et al. Vitiligo-inducing phenols activate the unfolded protein response in melanocytes resulting in upregulation of IL6 and IL8. J Invest Dermatol. 2012;132(11):2601–2609
38.Van den Boorn JG, et al. Inflammasome-Dependent Induction of Adaptive NK Cell Memory. Immunity. 2016;44(6):1406–1421.
39.Wagner RY, et al. Altered ECadherin Levels and Distribution in Melanocytes Precede Clinical Manifestations of Vitiligo. J Invest Dermatol. 2015 Jul;135(7): 1810–9.
40.Wang X, et al. Increased Expression of CXCR3 and its Ligands in Vitiligo Patients and CXCL10 as a Potential Clinical Marker for Vitiligo. Br J Dermatol. 2016
41.Wu S, et al. Use of permanent hair dyes and risk of vitiligo in women. Pigment Cell Melanoma Res. 2015;28(6):744–746.
42.Yang L. et al. Interferon-gamma Inhibits Melanogenesis and Induces Apoptosis in Melanocytes: A Pivotal Role of CD8+ Cytotoxic T Lymphocytes in Vitiligo. Acta Derm Venereol. 2015 Jul;95(6):664–70
43.Yu R, Broady R, Huang Y, Wang Y, Yu J, Gao M, et al. Transcriptome analysis reveals markers of aberrantly activated innate immunity in vitiligo lesional and non-lesional skin. PLoS One. 2012;7(12): e51040.
44.Yusupova L.A., Yunusova E. I., Garaeva Z. Sh., Mavlyutova G. I. Modern approaches to external therapy of patients with vitiligo // Practical medicine. 2014. No. 8 (84). pp. 24-26.

СОВРЕМЕННЫЕ ВЗГЛЯДЫ НА ПАТОГЕНЕЗ ВИТИЛИГО

Мавлянова Ш.З., Шукуров И.Б., Яхшиева М.Ф.

Резюме. *Витилиго является самым распространенным в дерматологии гипомеланозом, классифицируется как аутоиммунное генетически опосредованное заболевание, связанное с факторами окружающей среды, метаболическим и окислительным стрессом, активностью иммунной системы и аномалиями строения клеток. Статья носит обзорный характер, в ней освещены современные данные о патогенезе витилиго.*

Ключевые слова: *витилиго, окислительный стресс, Т клетки памяти, врожденный иммунитет, адаптивный иммунитет, регуляторные Т клетки.*