



Vitiligo: discoveries in its pathogenesis and new therapies

Vitiligo: descobertas em sua patogênese e novas terapias

Carolina Silva Poiani¹, Gisele Moss Troiano¹, Inácio Skraba Silva¹, Johann Costa Migliorini¹, Maria Clara Messias Gomes¹, Rafaela Precoma Erdmann¹, Irlena Monica Wisniewska de Moura¹

ABSTRACT

Introduction: Vitiligo is an autoimmune disease characterized by the progressive loss of melanocytes, resulting in hypochromic and achromic skin patches. It affects 0.4–2% of the global population and is more prevalent in women and Africans, and less in Europeans and Asians.

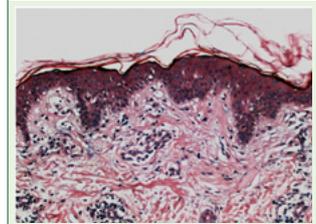
Objective: To review its mechanisms and analyze the main hypotheses underlying its manifestation and existing treatments.

Method: Narrative review searching for articles published between 2008 and 2023 in PubMed, Researchgate, Google Scholar, and SciELO.

Result: Ten articles were selected, emphasizing new pathophysiological hypotheses and current therapeutic approaches.

Conclusion: Vitiligo is an autoimmune disease involving genetic predisposition, oxidative stress, and abnormal immune responses. Therefore, the complexity of the mechanisms underlying the disease presents a challenge for therapeutic strategies. Current therapies aim to halt lesion progression and promote repigmentation depending on the clinical manifestation and location of the patches.

KEYWORDS: Vitiligo. Therapeutics. Pathology. Autoimmunity.



Marchiolo et al.³

Central Message

Vitiligo is an autoimmune disease characterized by the progressive destruction of melanocytes caused by the presence of excess cytotoxic lymphocytes (TCD8+), which leads to the appearance of hypochromic and achromic spots on the skin. Thus, examining its pathophysiological mechanisms, exploring the main hypotheses about its causes, and analyzing the currently available treatments is pertinent to the present day.

Perspective

Vitiligo is a multifactorial disease involving genetic factors, oxidative stress, and abnormal immune responses. Its treatment follows 3 main approaches: use of topical corticosteroids, nbUVB therapy and excimer laser. These therapies aim to interrupt the progression of lesions and promote repigmentation, varying according to the clinical manifestation and location of the macules.

RESUMO

Introdução: Vitiligo é doença autoimune caracterizada pela perda progressiva de melanócitos no organismo, resultando em manchas cutâneas hipocrômicas e acrômicas. Apresenta-se em 0,4-2% da população mundial, é mais prevalente em mulheres e nos africanos, e menos em europeus e orientais.

Objetivo: Revisar os seus mecanismos e analisar principais hipóteses atribuídas à sua manifestação e tratamentos existentes.

Método: Revisão narrativa com busca de artigos publicados entre 2008 e 2023 no Pubmed, Researchgate, Google Acadêmico e SciELO.

Resultado: Foram selecionados 10 artigos com ênfase nas novas hipóteses fisiopatológicas e abordagens terapêuticas atuais.

Conclusão: Vitiligo é doença autoimune que envolve predisposição genética, estresse oxidativo e respostas imunológicas anômalas. Portanto, a complexidade dos mecanismos subjacentes à doença é desafio frente às estratégias terapêuticas. As terapias atuais visam interromper a progressão das lesões e promover a repigmentação conforme a manifestação clínica e localização das máculas.

PALAVRAS-CHAVE: Vitiligo. Terapêutica. Patologia. Autoimunidade.

¹Evangelical Mackenzie Faculty of Parana, Curitiba, PR, Brazil.

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INTRODUCTION

Vitiligo is an autoimmune disease characterized by the progressive loss of melanocytes in the body, resulting in the appearance of hypochromic and achromic spots in various regions of the skin.¹⁻³ This is a chronic condition that has 2 main clinical manifestations, divided into segmental vitiligo (SV) and non-segmental vitiligo (VNS).^{2,4} The first form is usually presented in a linear or block area of the body.^{2,4} VNS, on the other hand, includes other forms such as focal, mucous, acrofacial, generalized, universal, mixed, and other rare forms whose main characteristic is the presence of bilateral macules or spots on the body.^{2,4} Vitiligo affects 0.4-2% of the world population and its prevalence is very variable, being higher in Africans and Europeans and lower in Orientals.^{2,3} According to the Brazilian Society of Dermatology, in 2019, population prevalence in some countries in the world was: China, 0.09%; Denmark, 0.38%; United States, 0.40-2%; India, 1.13%.⁵

The objective of this study was to review and update the pathophysiological mechanisms of vitiligo, analyzing the main hypotheses attributed to the manifestation of the disease and the existing treatments.

METHOD

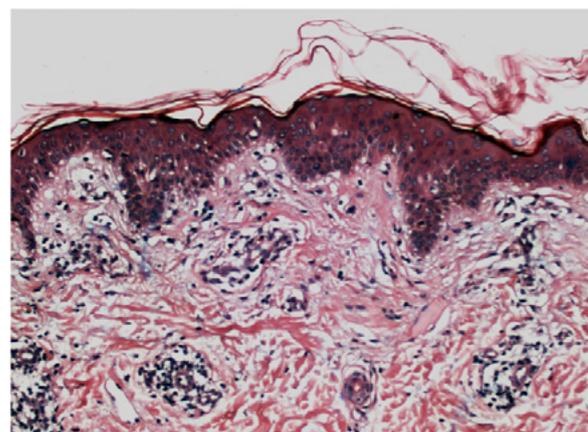
Narrative review with search of articles published between 2008 and 2023 in the following databases: Pubmed, Researchgate, Google Scholar and SciELO. After reading the titles and abstracts, those that did not adequately meet the objectives of this research were excluded, and 10 articles were selected with an emphasis on those that presented the pathophysiological hypotheses and therapeutic approaches from the years 2015 to 2023. The inclusion criteria involved in the selection of articles were articles published in the last 10 years and that addressed the desired content of pathophysiology and therapy. The research involved the descriptors "vitiligo", "therapeutics", "pathology" and "autoimmunity".

DISCUSSION

Vitiligo is chronic acquired dyschromia that results in the loss of melanocytes in the basal layer of the epidermis and the consequent loss of pigmentation of the affected areas.^{3,6,7} The characteristic lesions are calcareous, amelanotic, non-scaly white macules with varied borders.⁷ They can be found all over the skin and areas of the mucous membrane, including the possible involvement of hair follicles, and may be accompanied by systemic manifestations such as sensorineural deafness, uveitis, thyroiditis.³ The distribution patterns and clinical characteristics of vitiligo allow us to classify its manifestation into SV and VNS.⁴ While SV is present in a unilateral body area, in a linear fashion or in blocks tending to stabilization, the other type is more predominant and manifests symmetrically, usually on the extensor and flexor surfaces, and the lesions tend to evolve over time.⁴ VNS can also present itself in various forms such as acrofacial, mucosal, generalized, and

universal.⁴

From the histopathological point of view, its lesions affect both the epithelium and the superficial portion of the dermis.³ In the basal layer of the epidermis, there is a significant reduction in melanin and melanocytes present, as well as the presence of lymphocytic inflammatory infiltrate, with TCD3+ and TCD8+ lymphocytes predominating in perivascular areas of the dermis (Figure 1).³ In addition, there is an increase in the number of Langerhans cells in the epidermis, melanocytes with short dendrites and few melanosomes, and vacuolization of melanocytes in the basal layer of the epidermis.³ Among other alterations found are the thickening of the basement membrane and stratum corneum of the epidermis, with larger corneocytes as a way of compensating for the decrease in keratinocytes in areas with vitiligo.³ Lesions may also present acanthosis and defects in the adhesion elements between keratinocytes and/or melanocytes, such as E-cadherins, hindering cell adhesion.³



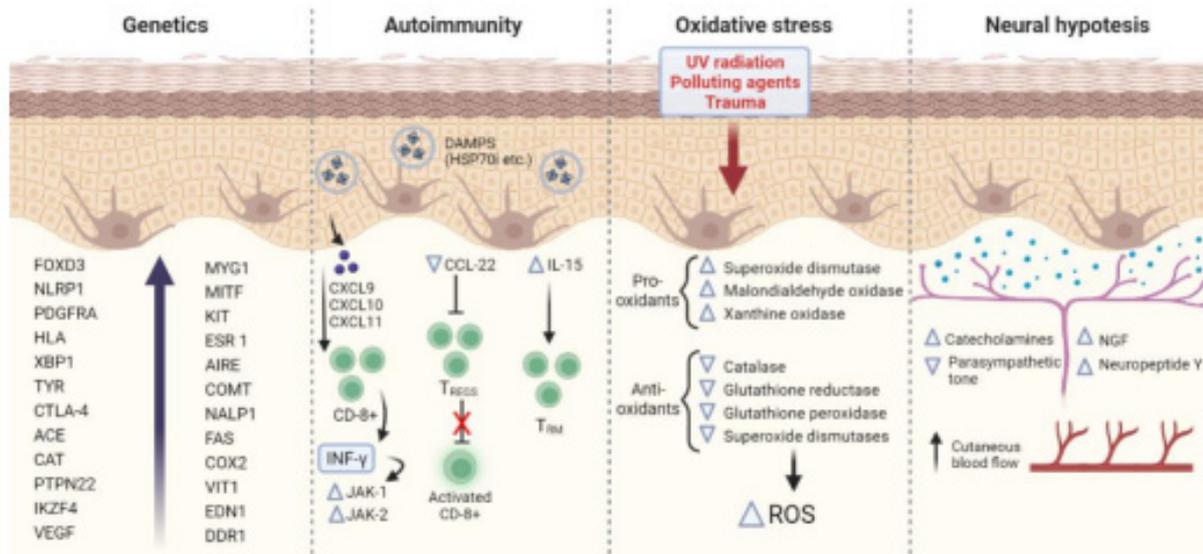
Source: Marchioro et al.³

FIGURE 1 – Active vitiligo (H&E×40)

The pathophysiology of vitiligo is multifactorial, encompassing several factors, including genetic, autoimmune, environmental, and neural, resulting in the elaboration of several hypotheses to try to explain its pathogenesis (Figure 2).⁶

One hypothesis suggests that genetics plays a significant role in the incidence.³ It is estimated that between 75-83% of affected individuals have components of genetic inheritance.³ Because it is a multifactorial disease with polygenic pattern inheritance, the genetic mapping for the analysis of risk factors is extensive and covers several genes whose expression may be associated with vitiligo.³ Among these genes, the transcription factor XBP1 located on chromosome 22q12 stands out.^{3,8,9} It regulates the expression of genes such as HLA class II, which is often related to autoimmune diseases, vitiligo being an example.^{3,8,9} In residues 135 for HLA-DQB1 and 46 for HLA-B, changes in amino acids were found that indicate increased susceptibility in the Chinese population.^{3,8,9} In addition, 3 loci in 1p31.3 – p32.2, 7q21.¹¹ and 8p12 were associated with increased vulnerability in Europeans and loci 4q13-q21 in the Asian population.^{3,8,9} Of these described, FOXD3 was the gene present at loci 1p31.3–p32.2 and PDGFRA

Vitiligo pathogenesis



Source: Diotallevi et al.⁶

FIGURE 2 – Theories of the pathogenesis of vitiligo

at loci 4q13–q21.^{3,8,9} In addition to those mentioned above, HLA-A*33, HLA-Aw*31, HLA-DR4, HLA-DR7 and HLA-DQB1*0303 have been identified as risk factors for vitiligo in different populations.^{3,8,9}

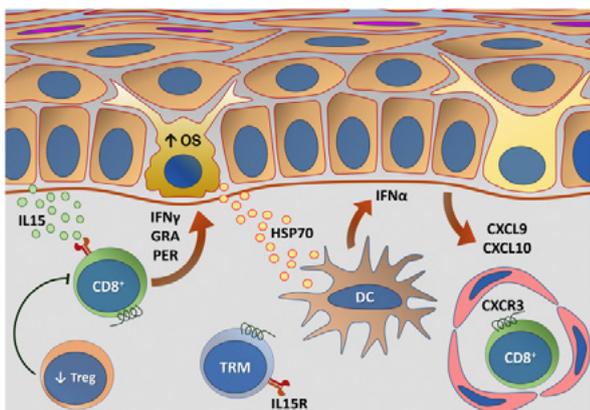
Another hypothesis to explain the pathogenesis of vitiligo, determining a crucial point at the beginning of the symptomatology, would be the interaction of melanocytes with reactive oxygen species (ROS), such as O₂⁻ and H₂O₂, in a process of oxidative stress.² From the perspective of the affected organism, the accumulation of ROS occurs both by external factors, such as exposure to ultraviolet radiation (UV) and medications, and by internal factors, due to genetic propensities that stimulate the production of these molecules in metabolic reactions with high mitochondrial demand.² In particular, melanocytes act as instigators and victims of oxidative stress, as the process of melanogenesis results in significant amounts of O₂⁻ and miscoiled proteins, favoring a pro-oxidative environment.² Consequently, there is hyperactivity of the enzyme superoxide dismutase 2 responsible for degrading the O₂ into H₂O₂ and O₂.² This enzyme is also related to the reaction of unfolded proteins, while the main lines of defense against the imbalance between oxidants and antioxidants, such as glutathione and NFR2, have limited effects on the disease.¹ In addition, in vitiligo there is a dysregulated redox balance associated with low expression of catalase, an enzyme that protects cells from ROS.² Thus, the state of oxidative stress and continuous inflammation increase the cytotoxicity of melanocytes, causing apoptosis of these cells at pathological levels even in the subclinical period.² The accumulation of reactive oxygen species can trigger changes in the endoplasmic reticulum of the melanocyte, resulting in the accumulation of defective

proteins and activating the cellular stress phenomenon known as the misfolded protein reaction.^{2,6}

Additionally, one of the main hypotheses widely investigated in the pathophysiology of vitiligo is the relationship with autoimmunity.^{2,3} The pathogenesis of this disease is marked by the participation of the innate immune system. In vitiligo lesions, dendritic cells, macrophages and Natural Killer cells can be found.³ In addition, there is the presence of pro-inflammatory cytokines characteristic of innate immunity, such as interleukins 6, 8, 12, and 15 and tumor necrosis factor alpha.^{2,3} One of the major hypotheses is that oxidative stress in melanocytes stimulates the secretion of exosomes containing chaperone proteins and molecular patterns associated with damage, and thus delivering self-antigens to dendritic cells that undergo maturation into antigen-presenting cells.^{2,3} The molecular pattern associated with damage with greater relationships with vitiligo is Heat Shock 70 chaperone.^{2,3} They are extracellular proteins that prevent protein misfolding and have the potential to induce the maturation and activation of dendritic cells.^{2,3} However, under conditions of physiological stress, they can be secreted by cells and released into the extracellular medium.³ Thus, its recognition by immune cells results in signaling for the release of cytokines such as interferon-alpha (IFN-alpha).³

This participation of the innate immune system also promotes the activation of the adaptive immune system.³ IFN-gamma produced by dendritic cells stimulates the production of chemokines such as CXCL9 and CXCL10 by keratinocytes, resulting in the recruitment of T cells.^{3,8} TCD8⁺ lymphocytes recruited to the epidermis and dermis cause damage to melanocytes through the release of perforins, granzymes, and proinflammatory

cytokines such as TNF-alpha and interferon-gamma, resulting in the destruction of these melanin-producing cells (Figure 3).³ Cytokines such as IFN-gamma, considered central to vitiligo autoimmunity, and TNF-alpha are significantly important in this context.³ IFN-gamma promotes the recruitment of autoreactive TCD8+ cells to the skin.³ These cells secrete greater amounts of this cytokine, which induce the production of CXCL9 and CXCL10 receptors by keratinocytes to recruit more T cells and promote the progression of vitiligo.^{2-4,8} When IFN-gamma is neutralized by antibody treatment or when T cells lack CXCR3 expression, autoreactive T cells are unable to migrate to the skin and therefore do not cause vitiligo.^{2-4,8} IFN-gamma regulation involves chemokine receptors and their ligands, such as CXCL9, CXCL10, and CXCL11.^{4,8}



Source: Marchioro et al.³

FIGURE 3 — Representation of changes related to the adaptive immunity of vitiligo

There is also the participation of neurological factors in vitiligo, both in clinical aspects, due to its presentation following the dermatomes in segmental vitiligo, and in general pathological mechanisms.^{3,6} Studies comparing the activity of the sympathetic nervous system in the skin between individuals with both presentations of vitiligo and patients without the condition concluded that segmental lesions showed up to 3 times greater activity of the local microcirculation, suggesting dysfunction of the sympathetic nervous system that would contribute to the pathophysiology of VS.^{3,6,10} Another factor would be the increased action of neuropeptides and neuronal growth factors around the areas of injury, which is associated with stressful situations.^{3,6,10} As a consequence, the joint occurrence of vitiligo and severe emotional stress can cause exacerbation of the condition, linking to other hypotheses about pathogenesis to explain the complex correlations in the affected metabolism.^{3,10}

The treatment of vitiligo depends on the manifestation of the disease.⁷ Treatments differ according to location and evolution, requiring follow-up and evaluation of 3-6 months after the beginning of the line of action.⁷ For its treatment, there are the 2021 British Association of Dermatologists guidelines, the 2023 German S1 guidelines, and the 2012 European Dermatology Forum consensus.⁷ They establish that both non-segmental and segmental vitiligo must follow 3 lines of treatment, with

some changes depending on the manifestation of the disease, in addition to psychotherapy and self-care with UV protection.⁷

For VNS, there are 3 possible objectives during the therapeutic procedure, which are stabilization, repigmentation and depigmentation.⁷ The first line consists of the use of topical corticosteroids (CTs) once daily.⁷ The second line provides nbUVB (narrowband UV-B) with or without CTs.⁷ In the third line, there are options such as excimer laser or light, plus CTs for localized disease.⁷ For adults with VNS in the hands and feet with inefficient response to other treatments, the third line is based on CO2 laser (1 time per month for 5 months) in combination with 5-fluorouracil (1 time per day for 7 days per month for 5 months).⁷

For VS, there are 2 main objectives, namely stabilization and repigmentation.⁷ The first line of treatment is the use of CTs once daily for up to 3 months.⁷ The second also consists of localized therapy with nbUVB.⁷ In case of progression under topical treatment, monochrome excimer or laser lamp is recommended.⁷ Otherwise, the laser or excimer is considered to be of the third line of treatment.⁷

CONCLUSION

Vitiligo is a complex and multifactorial autoimmune disease, characterized by the loss of pigmentation due to the decrease of melanocytes in the basal layer of the epidermis. It has 2 classifications: VS and VNS. Its etiology involves genetic predisposition, especially the transcription factor XBP1 located on chromosome 22q12; oxidative stress, resulting from the interaction between melanocytes and reactive oxygen species (ROS); and anomalous immune responses, marked by the presence of dendritic cells, macrophages, Natural killer and pro-inflammatory cytokines characteristic of innate immunity. In addition, sympathetic nervous system dysfunction may contribute to the pathophysiology of VS. Current therapies such as topical corticosteroids, narrow-band UVB phototherapy, and Excimer Laser, aims to interrupt the progression of lesions and promote repigmentation according to the clinical manifestation and location of the macules.

Authors' contributions

Carolina Silva Poiani – Research, Project Writing (original draft)
 Gisele Moss Troiano – Research, Project Writing (original draft)
 Inácio Skraba Silva – Methodology, Project Writing (original draft), Project Writing (review and editing)
 Johann Costa Migliorini – Conceptualization, Project Writing (original draft), Project Writing (review and editing)
 Maria Clara Messias Gomes – Research, Project Writing (original draft)
 Rafaela Precoma Erdmann – Conceptualization, Project Writing (original draft)
 Irlena Monica Wisniewska de Moura - Project Administration, Project Writing (proofreading and editing)

REFERENCES

1. Bergqvist C, Ezzedine K. Vitiligo: a review. *Dermatology*. 2020;236(6):571-92. <https://doi.org/10.1159/000506103>
2. Chang WL, Ko CH. The role of oxidative stress in vitiligo: an update on its pathogenesis and therapeutic implications. *Int J Mol Sci*. 2023;12(6):936. doi: <https://doi.org/10.3390/ijms24060936>
3. Marchioro HZ, Silva de Castro CC, Fava VM, Sakiyama PH, Dellatorre G, Miot HA. Update on the pathogenesis of vitiligo. *An Bras Dermatol*. 2022;97(4):478–90. <https://doi.org/10.1016/j.abd.2021.09.008>

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4. de Souza BRA, Ferreira JP, Besson JCF. Novas descobertas acerca dos aspectos imunológicos do vitiligo e sua relação com o biopsicossocial de mulheres acometidas. *Braz J Dev.* 2023;9(7):22804–20. doi: <https://doi.org/10.34117/bjdv9n7-114>
 5. Lamas M. Universidade de Santa Cruz do Sul. Departamento de Ciências da Vida. Curso de Biomedicina [dissertação]. Santa Cruz do Sul: UNISC; [data desconhecida]. Disponível em: <https://repositorio.unisc.br/jspui/bitstream/11624/2972/1/M%c3%a1rcia%20Costa%20Lamas.pdf>
 6. Diotallevi F, Gioacchini H, De Simoni E, Marani A, Candelora M, Paolinelli M, et al. Vitiligo, from pathogenesis to therapeutic advances: state of the art. *Int J Mol Sci.* 2023;24(5):4910. <https://doi.org/10.3390/ijms24054910>
 7. Marzano AV, Alberti-Violetti S, Maronese CA, Avallone G, Jommi C. Vitiligo: unmet need, management and treatment guidelines. *Dermatol Ther (Heidelb).* 2023;13(12):e2023316S. <https://doi.org/10.5826/dpc.1304s2a316s>
 8. Frisoli ML, Essien K, Harris JE. Vitiligo: mechanisms of pathogenesis and treatment. *Annu Rev Immunol.* 2020;38:621–48. <https://doi.org/10.1146/annurev-immunol-100919-023531>
 9. Spritz RA, Santorico SA. The genetic basis of vitiligo. *J Invest Dermatol.* 2021;141(2):265–73. <https://doi.org/10.1016/j.jid.2020.06.004>
 10. Mohammed GF, Goma AHA, Al-Dhubaibi MS. Highlights in pathogenesis of vitiligo. *World J Clin Cases.* 2015;3(3):221–30. <https://doi.org/10.12998/wjcc.v3.i3.221>