An overview on the effect of NLRP1 on inflammatory pathways in Vitiligo

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Abstract

Vitiligo is a skin disorder caused by the loss of melanocytes, the cells responsible for producing melanin. The loss of melanocytes results in the appearance of depigmented patches on the skin. The disease affects approximately 1-2% of the global population and does not show a preference for any specific age group or gender. The loss of melanin in the affected areas occurs due to the abnormal apoptosis, or cell death, of melanocytes. Vitiligo is classified as an autoimmune condition, in which the adaptive immune system becomes inappropriately activated and autoreactive CD8+ T cells mistakenly target and attack the body's own melanocytes. Currently, we lack a clear understanding of why the body specifically targets melanocytes and identifies them as foreign cells, mounting an immune response against them and activating apoptosis in the melanin producing agents. One recently identified candidate that has been implicated in the vitiligo immune response is the *NLRP1* gene. *NLRP1* is a crucial gene involved in the innate immune response, it codes for a protein that is associated with the regulation of inflammation. This gene plays a significant role in the assembly of the NLRP1 inflammasome, which is a multiprotein complex that activates inflammatory pathways in response to cellular damage caused by stress or infection. Research studies have revealed that there are differences in the NLRP1 expression and function in individuals affected by vitiligo, suggesting its potential involvement in the pathogenesis of the disease.

Keywords: Vitiligo, NLRP1, inflammasome, pathogenesis

Introduction

Vitiligo is a chronic autoimmune disease marked by the loss of skin pigmentation as a result of melanin depletion. Melanocytes, the cells responsible for melanin production, progressively diminish, resulting in the partial or complete loss of skin coloration[1]. It is important to acknowledge the global prevalence of this unpreventable disease. In a sample region of Denmark comprising 47,033 individuals, the prevalence of vitiligo was found to be 0.38%, with no significant differences in the distribution across five towns and between urban and rural areas[2]. A meta-analysis of 82 population or community-based studies revealed that the combined prevalence of vitiligo was 0.2% (95% confidence interval: 0.1%–0.2%). Notably, significant disparities emerged, with higher prevalence rates documented in the African and Indian regions. These disparities were highlighted in a study in 2012, which examined a population of 442 individuals in India and found the prevalence of vitiligo was 9.98%. Furthermore, a 2005 study of 2,871 individuals in Nigeria found that the prevalence was 3.17%[3]. The prevalence of vitiligo in both these countries is notably higher compared to the global rates.

Individuals with a family history of vitiligo face an elevated risk of developing the condition. Kin of people with vitiligo were shown to have a 6% chance of developing the condition while the risk for the general population is 1% or lower. Additionally, there is a 23% probability that twins will both have vitiligo if one of them develops the condition[4]. Nevertheless,the fact that the probability is not 100% suggests that there are additional factors that influence the onset of vitiligo. Several environmental factors have been proposed as potential triggers for vitiligo, including sunburn and exposure to certain chemicals. These factors may increase the risk of developing the conditions in those that are genetically predisposed.

This article will explore the role of the inflammasome NLRP1 in autoimmune diseases, with a specific focus on vitiligo. Additionally, it aims to inform readers of the importance of NLRP1 in advancing our understanding of autoimmune disorders.

Vitiligo Pathogenesis

Vitiligo pathogenesis is grounded on the immune system's misrecognition of melanocytes as foreign entities, leading to an orchestrated attack against these cells. This immune response is facilitated by the activation of T cells[1]. A T cell's role in the immune system is to identify specific antigens on foreign or abnormal cells. When these T cells come into contact with such antigens, they mount an immune response. This immune response is characterized by the secretion of signaling molecules called cytokines that function as messengers to control and direct immune responses[5]. When there is immune activation, pro-inflammatory cytokines are released, amplifying the immune response and encouraging the recruitment and activation of additional immune cells to the affected site.

Studies have revealed that in individuals with vitiligo, there is an overproduction of pro-inflammatory cytokines, including interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and notably, interleukin-2 (IL-2)[6]. The overabundance of these molecules has a

multifaceted impact, contributing to the disruption of the natural pigmentation process and the death of melanocytes through a process referred to as pyroptosis, a unique form of cell death associated with an inflammatory response.

One pro-inflammatory cytokine in particular, IL-2, is known for its essential role in stimulating the proliferation and differentiation of T cells, B cells, and natural killer cells, all of which constitute integral components of the immune system. More specifically, IL-2 acts as a growth factor for T cells, stimulating their replication and expansion in response to immune challenges. This function is crucial for mounting an effective immune response, as it ensures a rapid increase in the number of immune cells targeting the antigen. While IL-2's role in immune activation is significant, excessive production of this molecule contributes to inflammation and immune dysregulation. In the context of vitiligo, IL-2's overproduction is associated with the autoimmune attack on melanocytes.

The NLRP1 protein

Recent studies have shown that the *NLRP1* gene is upregulated in patients with familial vitiligo. This gene is located at chromosome 17 at position 13.2 and codes for the protein NLRP1[7]. NLRP1 is 1,473 amino acids long and has a molecular weight of 165.9 kDa[8]. This protein consists of multiple essential domains[9]. It features a Pyrin domain (PYD) which is responsible for protein-protein interactions, a NACHT domain crucial for detecting and terminating foreign entities within the body, Leucine-Rich Repeats responsible for recognizing molecular patterns, and a FIIND domain necessary for autoinhibition and activation, among others. Interestingly, NLRP1 has a unique interaction with Apoptosis-associated speck-like protein (ASC) involving the CARD domain for inflammasome assembly. Moreover, proteins with a Leucine-Rich Repeat or NACHT domain have been shown to be involved in apoptosis or inflammation[10]. NLRP1 is the only gene product of the *NLRP1* gene that has a Baculovirus Inhibitor of apoptosis protein Repeat (BIR) domain[11]. BIR domains work to inhibit apoptosis by directly interacting with caspases. These different domains form a complex protein structure with unique features.

The multiple protein domains of NLRP1 are crucial to the formation of the inflammasome complex and the triggering of the inflammasome cascade. The PYD domain facilitates the recruitment of caspase-1 and the activation of cytokines like IL-1 and IL-18. This domain also interacts with other PYD-containing proteins, such as ASC. The NACHT domain is essential for oligomerization and activation as well as nucleotide binding[12]. Additionally, this domain is key in spotting and halting foreign invaders in the body. This intricate formation of the inflammasome complex allows an organism to efficiently react to danger signals and mount an immune response.

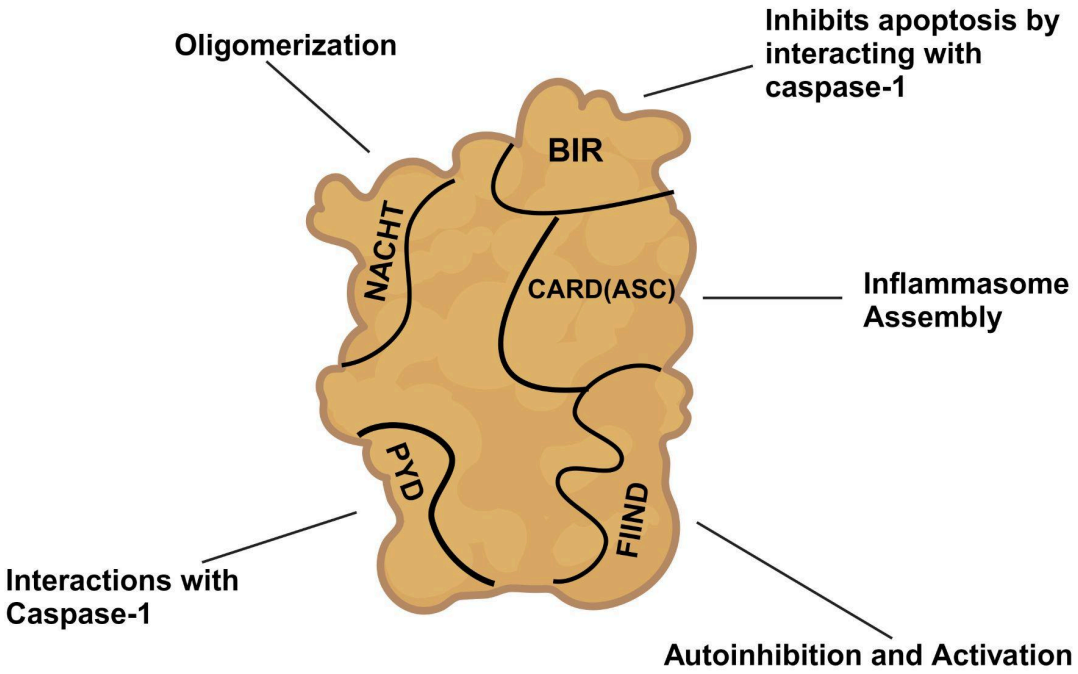

Figure 1. Domains of NLRP1 Protein Complex. Created using BioRender.com

The NLRP1 Inflammasome and Vitiligo

NLRP1 plays a pivotal role as an inflammasome component, driving innate immune responses and inflammation. NLRP1 acts as a scout for intracellular danger signals, it senses cellular stress, infections, or tissue damage. Upon recognition of these signals, NLRP1 undergoes oligomerization, assembling into a multiprotein complex known as the NLRP1 inflammasome. This inflammasome complex recruits adaptor proteins like ASC and facilitates the autoproteolytic cleavage of caspase-1, converting it into its active form. Caspase-1 contributes to inflammation by processing cytokines and triggering an immune response. Activated caspase-1 cleaves pro-inflammatory cytokines, including IL-1b and IL-18, into their active forms, enabling their secretion and driving inflammation. Furthermore, activation of the NLRP1 inflammasome leads to pyroptosis, a form of cell death characterized by membrane rupture and the release of pro-inflammatory cellular content. NLRP1's expression spans various tissues, with tissue-specific isoforms suggesting unique roles. The connections between NLRP1, inflammasomes, and autoimmunity are significant, as genetic polymorphisms in *NLRP1* have been linked to susceptibility to autoimmune diseases.

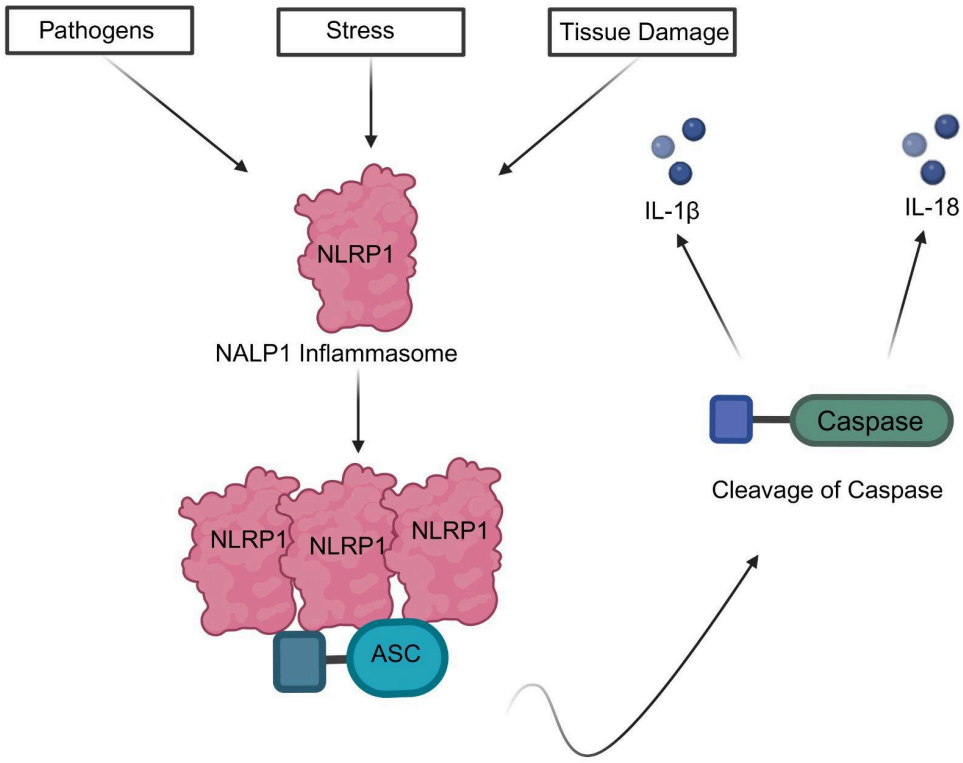

Figure 2. Oligomerization of the NLRP1 inflammasome. Created using BioRender.com.

Unsurprisingly, *NLRP1* is upregulated in vitiligo patients. Up-regulation of *NLRP1* can result in heightened immune surveillance and response efficiency. The protein's role in assembling inflammasomes facilitates the recognition of danger signals, any dysregulation of the inflammasome's sensing mechanisms could lead to abnormal activation of the immune cascade. This overactivity ultimately leads to the immune system's misrecognition of melanocytes as foreign entities. The hypersensitivity and elevated inflammation is at the core of vitiligo and many other autoimmune diseases.

The NALP1 Inflammasome and other autoimmune conditions

The NALP1 inflammasome has been associated with other autoimmune diseases. Genetic polymorphisms in the *NLRP1* gene affect immune signaling pathways, leading to dysregulation of immune responses directed at thyroid tissue, contributing to the development of autoimmune thyroid diseases[13]. Furthermore, studies have shown that NLRP1 contributes to the pathogenesis of Psoriasis[5]. Certain genetic variants of *NLRP1* are upregulated in patients with Psoriasis, a chronic inflammatory skin disorder. Rheumatoid Arthritis (RA) is another autoimmune condition that has been linked to the *NLRP1* gene. Genetic susceptibility studies have identified potential links between *NLRP1* polymorphisms and this disease. Variants of *NLRP1* contribute to the autoimmune responses and chronic inflammation characteristic of RA[14].

NLRP1 as a therapeutic target

The NLRP1 protein has been implicated in numerous autoimmune disorders, making it a candidate for the exploration of the molecular pathways dysregulated in these diseases. Disproportionate expression of *NLRP1* leads to excessive inflammation which is the basis of diseases including psoriasis and RA, both chronic autoimmune inflammatory diseases. In situations where inflammasome dysregulation is key to the development of the disease, inhibiting NLRP1 activity may be a candidate for a therapeutic approach. Gene therapy approaches could involve manipulating *NLRP1* expression to restore immune balance. In cases where *NLRP1* is under-expressed or dysfunctional, introducing functional copies of the gene could enhance immune responses and inflammatory control. In situations where *NLRP1* is over-expressed, inhibition could be used to prevent heightened immune activation. NLRP1's activity or expression is altered in vitiligo patients, therapeutic methods aiming to balance NLRP1's activity spare the demise of melanocytes.

Methods

The research was conducted through a systematic literature review of relevant articles in the field of inflammation in Vitiligo. The review aimed to identify and analyze studies that provided an outline for NLRP1 as a crucial inflammasome in Vitiligo.

I conducted a search of the following databases: Google Scholar, PubMed, and the NIH website. The search was performed from June 23, 2023 to October 10, 2023. The search strategy included a combination of keywords and controlled vocabulary terms surrounding the topic of NLRP1 and inflammation in Vitiligo.

Data were extracted from selected articles, including information on study design, participant characteristics, interventions, and outcome measures, as applicable.

Results

Vitiligo is a chronic autoimmune skin condition which can develop due to a combination of genetic and environmental factors. Certain genetic variations influence immune regulation and response, making individuals more prone to developing autoimmune conditions like vitiligo. A large majority of immune traits are influenced by our genes, this means parental genetic contributions play a major role in susceptibility to this autoimmune disease. Environmental factors, such as exposure to certain chemicals, stress, or infections, also contribute to the triggering of vitiligo in genetically predisposed individuals.

The depigmentation of the skin and premature whitening of natural body hairs profoundly affects individuals with vitiligo, however, the precise mechanisms underlying this condition's attack on melanocytes remain unknown. This condition affects millions worldwide, yet its molecular mechanism of action remains elusive. Understanding the reasons why vitiligo uniquely targets melanocytes not only holds promise for advancing therapeutic approaches but also provides valuable insight into the mechanisms governing autoimmune disorders.

Discussion

Bergqvist and Ezzedine (2020)[1]: Provided a general review of vitiligo, emphasizing its prevalence, impact, and the depletion of melanocytes.

Howitz (1977)[2] and Zhang et al. (2016)[3]: Highlighted the global prevalence of vitiligo and variations across different populations, shedding light on the importance of understanding its epidemiology.

Frisoli et al. (2020)[4]: Discussed the role of genetics in vitiligo, indicating that individuals with a family history of vitiligo face an elevated risk.

Ekman et al. (2014)[5]: Examined genetic variations of NLRP1 in psoriasis, underlining the role of cytokines and the immune response in autoimmune skin disorders.

Custurone et al. (2021)[6]: Explored the role of cytokines in vitiligo pathogenesis, focusing on IL-2 and its impact on immune dysregulation.

UniProt and NLRP1 Gene [7-9]: Provided information on the structure of the NLRP1 protein, including its various domains, which is crucial for understanding its function.

Micheau & Tschopp (2003)[10]: Discussed the role of NLRP1 in inflammasome formation and its association with autoimmune diseases like psoriasis.

Herman et al., (2009)[11]: Provided the structural characteristics of BIR domains in humans and the modular nature of IAP proteins, important for understanding inflammasome regulation.

Pelegrin, (2022)[12]: Provided information on the effects of NACHT domains in inflammasomes.

Alkhateeb et al. (2013)[13]: Linked NLRP1 genetic polymorphisms to autoimmune thyroid diseases, expanding the discussion to other autoimmune conditions.

Abdullah et al. (2023)[14]: Connected NLRP1 polymorphisms to rheumatoid arthritis, demonstrating the gene's broader implications in autoimmune responses.

Nadesalingam et al. (2016)[15]: Provided potential therapeutic approaches involving NLRP1, highlighting the gene's candidacy for targeted interventions.

The NLRP1 Gene Homepage (2013)[16]: Provided additional genetic information on NLRP1 and its variants.

Conclusion

This paper aimed to provide an overview of vitiligo, a skin condition distinguished by a loss of skin color and patches of depigmentation. The disease affects approximately 1-2% of the global population, and is an autoimmune condition where autoreactive CD8+ T cells target and attack melanocytes, leading to apoptosis and a loss of melanin. The mechanisms triggering the immune response against melanocytes remain unknown. A gene involved in the vitiligo immune response is the *NLRP1* gene, crucial in the innate immune system, associated with inflammation regulation, and codes for the NALP1 inflammasome. Variations in NALP inflammasome expression and function observed in individuals with vitiligo suggest a potential role in the disease's pathogenesis. Insight into the involvement of NLRP1 in vitiligo provides a foundation for further research and a deeper understanding of the mechanisms underlying Vitiligo.

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