Journal of Clinical and Biomedical Sciences

Review Article

Molecular factors in the development of vitiligo

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Abstract

Vitiligo is a chronic autoimmune disease, caused due to selective destruction of melanocytes. It is characterized by depigmentation of skin. The mechanisms that underlie this phenomenon has not been clearly understood. Therefore, the aim of this review was to collate all the emerging information regarding the involvement of molecular components in vitiligo pathogenesis. Initial surveys suggested that certain chemicals were responsible for causing this skin disease. Recent genetic studies like twin studies show that vitiligo arises due to hereditary factors. Certain predisposing risk variants have been identified through candidate gene studies and Genome-Wide Association Studies (GWAS). Skin biopsies and peripheral blood of vitiligo patients have revealed the presence of melanocyte targeting autoantibodies, increased T-cells and high levels of inflammatory cytokines, indicating that both humoral and cellular immunities play a major role in selective destruction of melanocytes. In addition to this, studies have shown the association of vitiligo with other autoimmune diseases, implicating that complications of other autoimmune diseases could lead to the development of vitiligo. Further research is required to understand the immune pathway of vitiligo and its commonness with other autoimmune disorders. This would help in tackling the disease therapeutically.

Keywords: Vitiligo, Genetics, Autoimmunity, Human Leukocyte Antigen, Cytokines

Introduction

Vitiligo is a cutaneous, chronic inflammatory autoimmune disease, caused due to selective destruction of melanocytes. It is characterized by the loss of pigmentation of the skin, oral mucosa and hair .[1] It can affect all age groups in a population, irrespective of gender .[2] It affects about 1% of people worldwide .[3] The prevalence in India is around 8.8 % .[4] Vitiligo does not cause any major debilitating condition in the patients. However, it affects the quality of life and mental health of the patient due to the social and cultural stigma .[5] This stigma has affected their lifestyle in such a way that patients develop psychological stress, anxiety, depression, lack of self-confidence and many mental issues .[6] Both environmental and genetic factors have been implicated in the induction of vitiligo. However, the nature of the interaction between these two factors is not clear. To tackle this disease therapeutically, one has to understand the molecular mechanisms and its interactions that underlie the disease pathogenesis. Therefore, the purpose of this review is to collate and summarize the molecular components and their mechanisms that could possibly participate in the pathogenesis of vitiligo, as this would help in understanding the disease more clearly.

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Conflict of Interest: None
Financial Aid: Nil

Role of environmental factors:

Phenotypic features and body conditions have been associated with vitiligo. Studies by Dunlap et al., showed that upper extremity moles, susceptible to tan, and history of blistering sunburn, are associated with the development of vitiligo .[7] Chemicals like monobenzone and rhododenol have been linked to occupationally induced vitiligo in industrial workers .[8]

Role of genetic factors:

The involvement of genetic components in the development of vitiligo has been highlighted by twin studies and familial aggregation studies. Das et al., studied the heritability of vitiligo in 298 pedigrees. It was found that the prevalence rate for this condition was around 2.7% among the relatives of probands. Considering the prevalence rate of vitiligo in the general population to be 0.46 %, the heritability of vitiligo was calculated and found to be around 46% .[9] Similar studies conducted by Sun et al., in the Chinese population and Alzolibani et al., in Saudi Arabian population were found to be 16% [10] and 54% [11] respectively. Furthermore, a twin study conducted by Alkhateeb et al., in Caucasian population showed that the concordance for vitiligo was 23% among 22 monozygotic twin-pairs and 0% among 24 dizygotic twin-pairs .[11]

Familial aggregation studies also showed that the prevalence of this disease is high among relatives .[12,13] Therefore, in general, first-degree relatives have a 6–7% risk of developing generalized vitiligo. In addition, 20% of vitiligo patients and their first-degree relatives are prominently susceptible to other autoimmune diseases like autoimmune thyroid disease, rheumatoid arthritis, late-onset type I diabetes mellitus, psoriasis, pernicious anaemia, systemic lupus erythematosus, and Addison's disease .[11] Therefore, these studies provide an insight that genetic factors also play a key role in the pathogenesis of vitiligo. Furthermore, the genetics of vitiligo cannot be explained by simple Mendelian genetics, since it is characterized by incomplete penetrance, multiple susceptibility loci, and genetic heterogeneity factors .[14]

Genetic variants associated with vitiligo:

Two approaches viz., genome-wide association studies (GWAS) and candidate gene studies have been undertaken to elucidate the genetic landscape that predisposes an individual to develop vitiligo. The top variants identified by GWAS are listed in Table 1. A meta-analysis on GWAS conducted by Jin et al., showed about 23 – 37 novel significantly associated susceptibility loci. Most of these loci were in the genes that regulate immune response, apoptosis and melanocyte function. In addition, some of these loci were also found to be cis-expression quantitative trait loci (cis-eQTL) .[15]

Candidate gene studies have been undertaken with selected gene variants from various pathophysiological theories linked to vitiligo. This has resulted in the identification of susceptibility loci that are involved in the regulation of T cell function, melanocytes, gene transcription, and antigen processing. Candidate gene studies and their outcomes are summarized in Table 2.

Role of autoantibodies:

Majority of the autoimmune disorders occur due to the development of autoantibodies against host cells. Studies on vitiligo, have shown a similar phenomenon, where circulating autoantibodies like anti-thyroid peroxidase (anti-TPO) [41], IgA [42] and others that are against melanocytes were found to be high in the serum .[43,45] A recent meta-analysis on the same, showed that people with vitiligo had higher concentrations of anti-thyroglobulin (ATG) antibodies, antinuclear antibodies (ANA), anti-gastric parietal cell antibodies (AGPCA) and anti-adrenal antibodies compared to healthy individuals; providing an insight that vitiligo can also lead to development of other complex autoimmune disorders [46].

There is no clarity on the factors that induce the formation of these autoantibodies. The following factors are assumed to contribute to the formation of anti-melanocyte antibodies viz., (i) genetic predisposition to dysregulation of T cells, (ii) microorganisms expressing cross-reacting antigens, and (iii) dysregulated immune response to damaged melanocyte.

Role of Human Leukocyte Antigen (HLA):

HLA [Major Histocompatibility Complex (MHC) in humans] is a gene complex that codes, for specialized cell surface molecules that presents processed antigens to T-cell receptors. There are 9 types of HLA genes in total; (i) HLA-A, HLA-B, and HLA-C are categorized under MHC-I. (ii) HLA-DPA1, HLA-DPB1, HLA-DQA1, HLA-DQB1, HLA-DRA, and HLA-DRB1 are categorized under MHC-II. Because they are involved in antigen presentation, abnormal changes in the HLA can lead to dysregulation of an immune response against self-antigens. Of these, HLA-A, HLA-B, HLA-C, HLA-DQ, HLA-DR, and their subtypes are associated with the development of autoimmune disorders like Type 1 Diabetes, Rheumatoid arthritis, Ankylosing spondylitis, Grave's disease and many more .[47]

Association of these disorders with vitiligo has also been done. Haplotypes of HLA-A*02:01 gene promoter variant, were shown to upregulate the HLA-A gene expression leading to increase cell-surface presentation of autoimmune target antigens, facilitating melanocyte recognition by autoreactive cytotoxic T-cells.[48] HLA-DR which is normally known to play a role in the antigen presentation and T-cell activation was found to be highly upregulated in the perilesional skin of vitiligo patients .[49] In addition to this, the relationship between melanocytes and MHC-II has been established. It is shown that

melanocytes have phagocytic activity and present the antigens to MHC-II restricted T cells, contributing as a target cell for cell-mediated toxicity. [50-51] Furthermore, keratinocytes have shown to exhibit melanocyte antigens to MHC-II after phagocytosing melanosomes. [52] Therefore, melanocytes expressing HLA-DR may actively involve in innate immune response and can become a target for CD8+ T cells.

Role of cytokines:

A large body of evidence shows that cytokines mediate the destruction of melanocytes in vitiligo. The cytokine profile of vitiligo lesions are different from the encircling normal skin. Overall, there appears to be an imbalance between the cytokines that promote melanocyte growth and those that damage it. The expression of keratinocyte-derived cytokines like granulocyte monocyte colony-stimulating factor (GMCSF), fibroblast growth factor (FGF) and stem cell factor (SCF) is lower in vitiligo affected skin areas. On the contrary, the expression of IL-6 and tumor necrosis factor-a (TNF-α) is higher in the affected skin compared with perilesional, non-lesional, and healthy skin. [53] However, the mechanism by which IL-6 and TNF contribute to the development of vitiligo is not clear. These cytokines are assumed to deregulate tyrosinase activity and inhibit melanocyte proliferation. [54-56] Other cytokine levels have also been recorded to be higher in serum/tissue of vitiligo patients, but the mechanisms for their induction are yet to be elucidated. The summary of recorded cytokine levels is given in Table 3.

Association with other autoimmune diseases:

There are few studies that propose the idea of an association of other autoimmune diseases with vitiligo. Many investigators have documented the cases where vitiligo and other autoimmune diseases like autoimmune thyroid disease (Hashimoto's disease and Graves' disease), pernicious anemia, Addison's disease, systemic lupus erythematosus [66], rheumatoid arthritis, adult-onset type 1 diabetes mellitus, and psoriasis [67] have coexisted in patients. Recent study conducted by Gill L et al., in US population, showed that people with vitiligo had higher prevalence of thyroid disease (12.9%), alopecia areata (3.8%), inflammatory bowel disease (0.9%), pernicious anemia (0.5%), systemic lupus erythematosus (0.3%), Guillain-Barre syndrome (0.3%), discoid lupus (0.2%), linear morphea (0.2%), myasthenia gravis (0.2%), and Sjögren syndrome (0.2%).[68] Besides, it has been observed that patients having at least one comorbid autoimmune disease, tend to suffer from severe vitiligo compared with those who had no comorbid autoimmune disease .[68]

These comorbidities could exist because of two reasons;

(i) All the autoimmune diseases share a common mechanism for pathogenesis.

(ii) An autoimmune disease may develop into complications and become systemic, thereby affecting other organs as well.

Table 1: Vitiligo susceptibility loci identified by genome-wide association studies.

Susceptibility locus	Gene	Odds Ratio	P value	Function/Pathway
Rs3213758 [16]	KIAA1005	2.77	6.20×10^{-11}	Cell signal
rs7758128	C6orf10, BTNL2	2.19	3.29×10^{-16}	T cell regulation
rs11966200	HLA-C, HLA-B	1.90	1.48×10^{-48}	Antigen processing
rs3823355	HLA-A, HCG9	1.50	9.05×10^{-23}	Antigen processing
rs2476601	PTPN22	1.39	1.31×10^{-07}	T cell regulation
Rs117744081 [15]	CPVL	1.84	8.72×10^{-26}	Immune regulation
rs73456411	IL1RAPL1	1.77	7.34×10^{-10}	Neuron regulation
rs10200159	PPP4R3B	1.51	3.73×10^{-19}	Cell structure regulation
rs2476601	PTPN22	1.38	1.21×10^{-18}	T cell regulation
rs1635168	OCA2–HERC2	1.37	8.78×10^{-14}	Melanocyte function
Rs11966200 [17]	MHC region	1.90	1.48×10^{-48}	Antigen processing
rs2236313	RNASET2	1.20	9.72×10^{-17}	Cell survival
rs6902119	CCR6	1.17	9.09×10^{-8}	Immune regulation
rs11593576	ZMIZ1	0.88	5.01×10^{-3}	T cell regulation
rs9468925	HLA-C-HLA-B Region	0.74	6.13×10^{-24}	Antigen processing

Table 2: Candidate gene studies on vitiligo

Gene	**Population (Case/Control)**	**P value**	**Function/Pathway**
HLA-DRB4*0101 HLA-DQB1*0303 [18]	Dutch (150/240)	0.001 0.006	Antigen processing
HLA-DRB1*03, DRB1*04 HLA-DRB1*07 [19]	Turkish (41/61)	0.001 0.0002 0.0004	Antigen processing
DRB1A*04- (DQA1*0302)-DQB1*0301 [20]	Caucasian (76 families/ published reference std.)	<0.003	Antigen processing
CTLA-4 [21]	Turkish (36/100)	0.024	T cell regulation
ACE [22,23]	Korean (120/429) and South Indian (186/201)	0.012 0.008	Neurohumoral factor
CAT [24,25]	Caucasian (177/235) North India (80/30)	0.016 0.004	Cell survival
PDGFRA [26]	Chinese (480/480)	0.008	Cell survival
PTPN22 [27-29]	Caucasian (165/304) Romania (65/111) Tamilian (264/264)	0.006 0.013 <0.001	T cell regulation
MYG1 [30]	Estonian (124/325)	<0.05	Melanocyte regulation
ESR1 [31]	Korean (120/254)	0.013	Transcription factor
FOXD3 [32]	American family (1 family/100)	<0.001	Transcription factor
AIRE [33]	British (86/363)	0.003	Transcription factor
NALP1 [34]	Romania (66/93)	0.019	Immune system regulator
FAS [35]	Chinese Han (750/756)	0.007	Cell survival
EDN1 [36]	Korean (312/313)	<0.000	Cell regulation
COX2 [37]	Chinese (755/774)	0.004	Melanogenesis
GZMB [38]	Chinese Han (2147/973)	<0.000	Cell survival
TNFα [39]	Gujarat (977/990)	<0.000	Immune cell regulation
IL10 [40]	Hyderabad (130/150)	<0.001	Immune cell regulation

Table 3: Cytokine profile in vitiligo

Study population	Sample	Cytokine	Level(s) in cases	Reference
India	Serum	IL6, IL2, IFNγ and TNFα	High- IL6 and IL2 Low- IFNγ No significance- TNFα	[**57**]
Italy	Serum	IL23	High- IL23	[**58**]
India	Serum	IL-2, IL-4, TGF-β and IL-17	High- IL2, IL4 and IL17 Low- TGF-β	[**59**]
Egypt	Plasma/Serum and tissue	IL17 and TGF-β	High- IL17 Low- TGF-β Tissue- IL17	[**60-61**]
Iran	Plasma and PBMC	IL17A, IL22	High- IL22 and IL17 High mRNA expression- IL17A and IL22	[**62**]
Egypt	Serum and tissue	IL17	High- IL17	[**63**]
India	Serum	IFNγ and IL10	High- IFNγ Low- IL10	[**64**]
India	Serum	IL2, IL6, IL17, IL22, and TNF-a	High in localized- IL22, TNF-a High in generalized- IL6, IL17, TNF-a	[**65**]

Conclusion:

There are many theories that focus on the involvement of the immune response in the pathogenesis of vitiligo. It has been associated with other autoimmune diseases like thyroiditis, rheumatoid arthritis, psoriasis and many more, indicating that complications of other autoimmune disorders could also lead to the development of vitiligo. Several autoimmune diseases share some common genes that could be responsible for developing vitiligo. Molecular components like inflammatory cytokines, immune-regulatory genes, immune cells, and autoantibodies are also known to play a role in destroying melanocytes. However, the exact mechanism/ pathway for the induction of vitiligo is yet to be elucidated. Therefore, further research should focus on understanding the immune pathway of vitiligo and its commonness with other autoimmune disorders. This would enhance knowledge in understanding, not only the etiopathology of vitiligo but also help in formulating drugs that can ameliorate other similar autoimmune disorders.

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