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Review

A holistic review on the autoimmune disease vitiligo with emphasis on the causal factors

Seema Patel[a,*], Abdur Rauf[b,*], Haroon Khan[c], Biswa Ranjan Meher[d], Syed Shams ul Hassan[e]

[a] Bioinformatics and Medical Informatics Research Center, San Diego State University, 5500 Campanile Dr, San Diego, 92182, USA
[b] Department of Chemistry, University of Swabi, Anbar, 23561, K.P.K, Pakistan
[c] Department of Pharmacy, Abdul Wali Khan University, Mardan, 23200, Pakistan
[d] Centre for Life Sciences, Central University of Jharkhand, Brambe, Ranchi, 835205, Jharkhand, India
[e] Department of Marine Chemistry and Natural Products, Ocean College, Zhejiang University, Hangzhou, 310058, PR China

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ABSTRACT

Vitiligo is an idiopathic systemic autoimmune disease affecting skin, hair and oral mucosa. This genetic yet acquired disease characterized by melanin loss is a cause of morbidity across all races. Though thyroid disturbance has been recognized as a key trigger of this pathology, an array of other factors plays critical role in its manifestation. Multiple hormones (corticotropin-releasing hormone, adrenocorticotropic hormone, α-melanocyte-stimulating hormone, melatonin, calcitriol, testosterone, estrogen), genes (Human leukocyte antigen (HLA), Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), Forkhead box D3 (FOXD3), Cluster of differentiation 117 (CD117), Estrogen receptor (ESR) 1, Cyclooxygenase-2 (COX2), Vitiligo-associated protein 1 (VIT1)), and lifestyle choices (stress, diet, cosmetic products, and medications) have been suspected as drivers of this disorder. The pathological mechanisms have been understood in recent times, with the aid of genomic studies; however a universally-effective therapy is yet to be achieved. This review discusses these under-investigated facets of vitiligo onset and progression; hence, it is expected to enrich vitiligo research.

Contents

1. Introduction

Vitiligo, a systemic autoimmune disease affecting skin is a comparatively lesser-investigated pathology [1]. This disease, characterized by depigmentation or melanin loss, is mostly non-fatal, but it has its harmful consequences [2]. Depleted melanocytes (melanin cells) expose skin epidermis to UV light, which increases the chances of skin irritation and cancer. Also, the patchy

* Corresponding authors.
E-mail addresses: seemabiotech83@gmail.com (S. Patel), mashaljcs@yahoo.com (A. Rauf).

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appearance leads to psychological disturbance to the sufferer [3]. It leads to emotional distress, low self-esteem [4] and affects sexual life of the patients [5]. Often the affected persons, especially the children, get bullied and stigmatized [6]. This disease, also known as leukoderma is pervasive across all races, though instances are higher in some [7]. For example, the activity of tyrosinase, the enzyme responsible for catalyzing melanin synthesis, is higher in Black skin melanocytes [8], than that of Caucasian skin melanocytes.

This disease can appear at any age, though evidences suggest the higher chances of occurring before the age of 20 [9,10]. Symptoms of the onset include itching, and the development of whitish maculae on the skin [11]. The manifestation of the disease is variable such as generalized or segmental, where the former is symmetrical [12], and the latter affects only one lateral half of the body [13]. Depending on the distribution of white patches, the disease has been classified as vitiligo focalis (depigmentation in one area), vitiligo segmentalis (depigmentation in quasi-dermatomal pattern), vitiligo acrofacialis (depigmentation in face and distal extremities), vitiligo vulgaris (depigmentation all over the body), or vitiligo universalis (depigmentation of entire body) [14–17]. Vitiligo often co-exists with other autoimmune disorders, such as Sutton or halo nevus (mole surrounded by depigmented halo), and malignant melanoma [18,19]. At present, one percent (0.5–2%) of the total world population suffers or is prone to vitiligo [20].

Several genetic factors of vitiligo have been identified through gene expression, allelic association and genome-wide linkage studies [21]. The candidate genes span multiple chromosomes. Such genes include HLA, AIRE, VIT1, CAT, FOXD3, ESR1, COMT, PTPN22, NALP1, PDGFRA, MYG1, MITF, CD117, XBP1, FAS, COX2, EDN1 and ACE [22]. These genes are harbored in chromosomes 1 (COX2, FOXD3); 2 (VIT1/FBXO11); 4; 6 (HLA); 7; 8; 9; 14; 17 (NLRP1); 19; 21 (AIRE); and 22 (COMT) [22–26]. These findings justify the polygenic, familial clustering (non-Mendelian pattern) nature of vitiligo [22]. Genotyping studies have revealed several single-nucleotide polymorphisms (SNP) in the genes mentioned above, which might be linked to vitiligo.

Vitiligo is often associated with pernicious anemia, psoriasis, Addison's disease, rheumatoid arthritis, adult-onset insulin-dependent diabetes mellitus, systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), and infertility, thus forming a cluster of diseases with common genetic basis [27]. Sporadic vitiligo is associated with above-mentioned autoimmune pathologies and often manifest in blood relatives [27–29]. Its shared genetic basis with another severe autoimmune disease SLE has come forth [30]. Based on the evidences, the link between vitiligo and celiac diseases have been proposed [31].

Vitiligo has a complex etiology and unpredictable progression and cessation pattern, for it responds to a number of endocrine signals. Though several genes are responsible for this disease, their triggers can be variable. Psychological stressor (emotional strain) is one factor [32]. Stress products such as reactive oxygen species (ROS) can be produced by exogenous and endogenous stimuli [33].

There is no assured therapy available for vitiligo. However, some medications can restore the pigments. For immunosuppression, topical corticosteroids such as glucocorticosteroid (mometasone furoate), prednisolone and hydrocortisone are administered [34]. But, the steroid treatment can lead to side effects such as nausea, dizziness, erythema (redness or rash), itching, burning, skin thinning, skin atrophy, and telangiectasia (dilated capillaries visible through skin) [35–37]. Phototherapy includes light exposure and narrowband UV B laser radiation [38]. Calcipotriol (derivative of hormone calcitriol, a form of vitamin D) and psoralen (furocoumarins) with UVA light are often prescribed as non-surgical re-pigmentation therapy in vitiligo patients [18]. Calcineurin, a calcium-dependent serine/threonine protein phosphatase expressed by the neurons, cardiac cells, muscle cells, and lymphocytes has been discovered to play role in vitiligo pathogenesis [39]. To block its activity, calcineurin inhibitor (used for atopic dermatitis and lymphoma therapy) is used. Generic drugs of these inhibitors, such as tacrolimus and pimecrolimus, have been successfully used to treat vitiligo [39]. However, the inhibitor has been associated with side effects like posterior reversible encephalopathy syndrome (PRES), a cluster of health conditions including headache, seizures, lack of visual co-ordination, and altered consciousness [40,41]. For temporary camouflage, self-tanning dyes are administered. Potassium permanganate, indigo-carmine, Bismarck brown, and henna (*Lawsonia* sp.) paste are some of preferred tanning agents [42]. Dihydroxyacetone (DHS), a glycerone-based camouflage creams are popular. This triose sugar reacts with amino acid of the skin corneum by Maillard reaction, forming a brown-colored complex [43,44]. However, long-term usage of DHS puts additional stress on skin and causes toxicity Petersen et al. [44]. Cosmetic tattoos are another option, especially for masking depigmentation around the lips [45,46]. Surgical interventions through laser therapy and skin grafting are performed in some cases [47]. Antibiotic like pimecrolimus, from the ascomycin class macrolactam, are used in some cases for immunosuppression [48]. A monobenzone, 4-(Benzyloxy) phenol is used as a topical drug for medical depigmentation, which in case of extensive vitiligo, can be used to get rid of the remaining melanins, and to create a uniform melanin-free skin [49]. Unfortunately, none of these drugs or surgeries are side effect-free or affordable to all vitiligo patients. In this regard, a number of alternative medications have been suggested, such as the extracts from maidenhair tree (*Ginkgo biloba*) [50], flame vine (*Pyrostegia venusta*) [51] and tropical fern (*Polypodium leucotomos*) [52,53]. These botanical products cannot intervene at molecular level, but protect from photo-aging. Khellin (a natural furochromone vasodilator) 4% ointment, as a photosensitizer, has shown some degree of benefits [52,54,55]. Vitamins (B12, C, and E, folic acid) and minerals (zinc) are supposed to be beneficial for vitiligo alleviation [52,53]. Zinc being an antioxidant component, and anti-apoptotic factor, is suggested to be a skin favorable supplement [56]. The scope of amino acid L-phenylalanine as oral and topical therapy has been met with side-effect-free success [57].

However, for a disease that affects one among every hundred people, the existing therapeutic options are not efficacious enough. So, the molecular mechanisms of vitiligo need to be understood precisely.

A number of high-quality reviews focusing on different aspects of this disease, such as clinical variations, pathological mechanisms, therapeutic modalities etc. have been published [18,58]. This review discusses the latest developments on pertinent aspects of this disease, and suggests hypotheses which might be examined for a more efficacious treatment. Cochrane, MEDLINE, Embase, Pubmed databases have been referred to for the scientific literature discussed here.

1.1. Mechanisms of pathogenesis

Decades of intense research has led to the accumulation of immense insights on vitiligo. However, given its multifactorial, and multi-genic attributes, much remains to be unraveled. A synopsis of the key findings has been outlined below, before probing deeper.

Melanocytes, the highly differentiated, dendritic-shaped, pigment-producing cells of the follicular and interfollicular epidermis, produce a specialized lysosome-related organelle melanosome (others being lytic granules, MHC class II compartments, platelet-dense granules, azurophil granules, basophil granules etc.) [59]. Within the melanosome, melanin pigments are synthesized by