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Vitiligo - Part 1[*]

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Abstract: Vitiligo is a chronic stigmatizing disease, already known for millennia, which mainly affects melanocytes from epidermis basal layer, leading to the development of hypochromic and achromic patches. Its estimated prevalence is 0.5% worldwide. The involvement of genetic factors controlling susceptibility to vitiligo has been studied over the last decades, and results of previous studies present vitiligo as a complex, multifactorial and polygenic disease. In this context, a few genes, including *DDR1, XBP1 and NLRP1* have been consistently and functionally associated with the disease. Notwithstanding, environmental factors that precipitate or maintain the disease are yet to be described. The pathogenesis of vitiligo has not been totally clarified until now and many theories have been proposed. Of these, the autoimmune hypothesis is now the most cited and studied among experts. Dysfunction in metabolic pathways, which could lead to production of toxic metabolites causing damage to melanocytes, has also been investigated. Melanocytes adhesion deficit in patients with vitiligo is mainly speculated by the appearance of Köebner phenomenon, recently, new genes and proteins involved in this deficit have been found.
Keywords: Autoimmunity; Epidemiology; Genetic association studies; Genetic linkage; Vitiligo

INTRODUCTION

Vitiligo is a chronic systemic acquired disease that has an unpredictable clinical course, characterized by the appearance of macules and achromic or hypochromic patches on the skin and mucous membranes due to the disappearance of melanocytes in the affected area. These lesions can appear in different shapes and sizes and may be present in any area of the tegument.

Along with the skin and mucosal involvement, melanocytes in the ocular (predominantly in the uveal tract) and auditory apparatus (in vascular streaking and in the modiolus of the cochlea) can be decreased, ocular diseases such as uveitis or even neurosensorial hearing loss may also occur, being detected in 13 to 16% of patients in previous studies.[1-3] However, one of the major consequences of the disease is its psychological impact, since vitiligo can have strong effects on patients' self-esteem, with a subsequent increase in severe depression cases and a sharp sense of social discrimination resulting in quality of life deterioration.[4-6]

HISTORICAL ASPECTS

The oldest texts about a disease similar vitiligo as it is known today, date back to 1.500 BC and are present in Hindu sacred writings ("Vedas"), under the name *kilăsa*, and in texts (papyrus) from ancient Egypt.[7] There are several references in the Old Testament, especially in Leviticus XIII, to the term

Zoráat or Tzaraat, which in classical Hebrew means "white spots", but there is controversy as to whether this disease is really vitiligo.

The Latin term *vitiligo* was first used in the first century AD by Celsus in the classic treatise *De Medicina*, however, the Latin root of the word is unknown, and between the cited ones are some words with similar meanings, as *vitelius* and *vituli*, comparing the achromic or hypochromic lesions with vitiligo's white patches observed in calves, or *vitium* which means defect or flaw. [8]

In the nineteenth century, Brocq and Kaposi were among the first to describe both the clinical aspects, as achromia and hyperpigmentation at the borders of lesions, as well as its histopathology, in which Kaposi reported the absence of pigment granules in the basal layer cells of the epidermis. [9]

EPIDEMIOLOGICAL ASPECTS

The disease affects both genders equally, it can appear at any age, and the average age of onset is somewhat variable in different geographic regions. [10] The mean age ranging from 22 years in the U.S. and India, 24 in Brazil and 25 years old in England. Furthermore, differences in the mean age of onset have been reported among cases of sporadic and familial vitiligo. [11-13]

The prevalence of vitiligo has been estimated between 0.093% in China, 0.34% on the island of Martinique, 0.38% in Denmark, 1% in U.S. and 0.5% to 1.13% in India. [12, 14-18] Brazil has no updated epidemiological data on the incidence and prevalence of this disease.

With the disappearance of melanocytes in individuals affected by vitiligo, one would expect an increased incidence of non-melanoma cancer and actinic keratoses; however, experimental data show the opposite, leading some authors to hypothesize that this low incidence of skin cancer might be due to an overexpression in p53 protein which would have an anticancer effect, and immunohistochemical studies have already demonstrated the greater expression of p53 both in the affected and normal skin sections of vitiligo patients, compared to the skin of controls with a history of basal cell carcinoma. [19-23] Moreover, the reduced expression of GD3 (which contributes to keratinocyte apoptosis) induces a compensatory mechanism of epidermal thickening to protect the affected skin from UV radiation damage. [23] Finally, two recent retrospective studies have not detected a statistically significant increase of non- melanoma skin cancer (first study) or non-melanoma and melanoma skin cancers (second study) in patients with vitiligo, compared to the general population. Moreover, this last retrospective study, did not found a trend of increasing preva-lence of these skin cancers in the subgroup of patients treated with PUVA and Narrow-Band UVB, adjusted for age and time of exposure during life. [24, 25]

VITILIGO GENETICS

Most human diseases result from an interaction between genetic variants and environmental factors, and to establish the actual contribution of genetic factors is the first step of genetic studies that evaluate complex diseases. In general terms, the scrutiny of complex diseases genetic components begins through observational studies, such as: analyzes of pools of familial cases, comparative studies of concordance rates of disease occurrence among monozygotic (MZ) and dizygotic (DZ) twins and complex segregation analyzes (CSA). However, these studies do not provide information on the exact nature of the genetic component in question, as the location and identity of the involved genes. In order to advance it is necessary to perform different studies involving molecular genetic markers, as it is done in linkage and association analysis.

Genetic epidemiological studies have demonstrated that vitiligo can be considered a complex genetic disease because: (i) the disease varies in symptom severity and age of onset, which hinders the definition of the appropriate phenotype and the selection of the optimum study population; early age of onset was associated with familial occurrence of generalized vitiligo. [11,26] In addition, early onset vitiligo is associated with more severe disease; [11] (ii) the etiological mechanisms of the disease can vary; vitiligo's etiopathogenesis has not yet been fully clarified, and several theories have been proposed; (iii) complex genetic diseases are often oligogenic or even polygenic and each gene contributes to a fraction of the overall relative risk; linkage analysis performed using vitiligo phenotype identified susceptible *loci* located on chromosomes 1, 4, 6, 7 , 8, 17 e 22 co-segregating with the disease. [27-35] For these regions, some genes consistently associated with vitiligo have been reported, such as *NLRP1 (17p13) and XBP1 (22q12)*. [36, 37]

OBSERVATIONAL EPIDEMIOLOGICAL GENETICS IN VITILIGO

The involvement of genetic factors in the susceptibility to vitiligo became evident in familial studies, which demonstrated that vitiligo segregates with a complex standard of multifactorial and polygenic inheritance. [10] A study, involving 160 American Caucasian families, confirmed familial aggregation of cases with 20% of the affected individuals presenting at least one first-degree relative with vitiligo. [10] The relative risk of vitiligo in Denmark and India populations was seven for parents, 12 for siblings, and 36 for off-

spring.[10] The relative risk of vitiligo in first-degree relatives was estimated at between seven to 10 times higher than in general population.[38] A study about vitiligo conducted in twins showed 23% agreement rate of generalized vitiligo for 22 pairs of MZ twins compared with 0% in 24 pairs of DZ twins.[11] However, the lack of complete agreement for vitiligo between MZ twins suggests the importance of non-genetic factors.

Additional evidence for a genetic susceptibility component in vitiligo has been gathered from CSA, the main statistical tool used to determine, from familial information, the inheritance model that best explains the pattern of segregation on a particular phenotype.[39] Results of CSA held in 56 multigenerational Colombian families containing individuals affected by vitiligo indicated as the most appropriate model, the one that assumes the existence of a dominant major gene with strong influence of environmental factors acting on the recessive genotypes.[40] Another CSA involving 2.247 Chinese vitiligo patients and their families demonstrated that different types of vitiligo are regulated by different sets of genes, reinforcing the oligogenic/polygenic nature of the disease.[41]

LINKAGE STUDIES IN VITILIGO

Linkage analysis is a tool that allows the screening of the entire human genome, using multigenerational families in order to identify genomic regions that harbor *loci* responsible for the observed phenotype, even without prior assumptions about the disease pathogenesis. The principle of linkage analysis is based on the premise that if a polymorphic marker is near the *locus* that harbors the disease predisposing gene, they will co-segregate in families over generations, more intensively than expected under the hypothesis of aleatory transmission expected in an independent heritage of unconnected *loci*.[42]

The first evidence of linkage was between vitiligo associated with systemic lupus erythematosus (SLE) and chromosome 17p13 markers, a *locus* denominated by authors as *SLEV1*, in 16 Euro-American families affected by both diseases.[43] This result suggests the existence of a probable common genetic autoimmunity determinant of vitiligo and SLE in these families. A subsequent independent study detected linkage between 1p31 *locus*, termed by the authors "AIS1" (Autoimmunity Susceptibility Locus 1) and vitiligo in a large multigenerational family presenting multiple cases of vitiligo and Hashimoto's thyroiditis.[44,45] In a subsequent complementary study, in which the original collection of families was expanded to a total of 102 pedigrees, additional evidence of the connection with vitiligo was detected on chromosomes 7 and 8. Furthermore, the evidence of linkage to 17p13 *locus* previously described was confirmed.[34] Thus, the suggestive linkage signal to four *loci* on chromosomes 9, 13, 19 and 22 was detected.[33] The authors suggest that linkage signals detected for chromosomes 7q and 17p seem to derive primarily from families segregating vitiligo and epidemiologically related autoimmune diseases. On the other hand, the linkage signal detected for chromosome 8p derived from families that segregate only vitiligo.[33] More recently, a genomic scan conducted in Chinese multiplex families affected by generalized vitiligo identified the connection between the disease and markers of region 4q13-q21, 22q12 and 6p21-p22.[34, 35]

Linkage analyzes performed in populations with different ethnic backgrounds, using generalized vitiligo as phenotype, showed that the main susceptibility *locus* co-segregating with the disease is not the same in each population, except for 22q11. This suggests that different genes may be involved in the pathogenesis of vitiligo in different populations around the world, characterizing a polygenic disease.[33-35] The exact definition of the gene or genes involved in controlling the phenotype in question depends on further studies, usually association ones, involving target genes located in genomic regions identified in the linkage analysis.

ASSOCIATION STUDIES IN VITILIGO

There are two main design types of association studies: population-based and family-based. Population-based studies (case-control) primarily compare the allele frequencies of a genetic marker among affected and unaffected individuals (controls); a particular allele is considered associated with the studied phenotype when it occurs with different frequencies amongst the groups. The big challenge in this type of study is the correct selection of the population segment and the sample size, in order to have sufficient power to detect the genetic effect, if it really exists. Family-based association studies use the basic trio design, consisting of two parents and an affected offspring. The analysis assesses the frequency with which a particular allele is transmitted from a heterozygous parent to the affected child: a deviation in the expected aleatory transmission, according to the first law of Mendel, suggests an association. It is important to emphasize that, association studies have greater power to detect moderate to weak genetic effects when compared to linkage studies, which makes them ideal for fine mapping of previously detected chromosomal regions connected with the disease.[46]

Currently, over 50 candidate genes were already investigated in association studies for susceptibility to vitiligo. However, few genes, including *DDR1*, *XBP1*, *NLRP1*, *PTPN22* and *COMT*, were consistently associated with the disease, either by being located in a

region previously identified in a linkage study (positional) or by having been replicated in populations of different geographic regions, as described in table 1. In addition to the genes listed above, an evidence of association with vitiligo phenotypes was found for markers of *ACE, AIRE, CD4, COX2, ESR1, EDN1, FAS, FOXD3, FOXP3, IL1-RN, IL-10, MBL2, MC1R, MYG1, Nrf2, PDGFRA, PRO2268, SCF, SCGF, TXNDC5, UVRAG* and *VDR* genes, but these associations were not replicated in independent populations.[47] Nevertheless, several genetic studies for *CAT* and *CTLA-4* genes in populations of different ethnic origins, have produced conflicting results.[47-53] In general, associations between variants of *HLA* genes with susceptibility to vitiligo, considering different ethnic groups, have not been consistent, however, there are notable exceptions, such as the association signs observed for *HLA-A2, HLA-DR4* and *HLA -DR7* alleles.[27, 54-58]

Candidate genes identified from linkage genomic scans generated interesting results. The first

TABLE 1: Non-HLA genes consistently associated to vitiligo

Gene	Region	Study design	Sample case/control Families (Ind)	Population	Phenotype	Variant	Position	P-Value	OR (CI - 95%)	Author	Year
COMT	22q11.1-q11.2	C C	50 / 66	Turkish	Acrofacial	val108/158met	Exon 3	P=0.047	NA	Tursen et al,	2002 [131]
		C C	749 / 763	Chinese	Vulgaris / localized - IIP	rs4680	Exon 3	P<0.001	1.42 (1.15 - 1.75)	Li et al,	2009 [132]
		C C	1392 / 2629	European	Generalized	rs4680	Exon 3	NS	-	Birlea et al,	2011 [47]
DDR1	6p21	B F	188 F (596 IND)*	Brazilian	Vitiligo per se	rs4618569	5`Near Gene	P=0.002	5.27 (1.59 - 17.40)	Silva de et al,	2010[61]
						rs1049623	Exon 15	P=0.05	1.73 (0.97 - 3.08)		
						rs2267641	Exon 17	P=0.01	3.47 (1.22 - 9.17)		
		C C	134 / 134	Brazilian	Vitiligo per se	rs2267641	Exon 17	P=0.04	6.0 (1.73 - 52.33)	Silva de et al,	2010 [61]
		C C	220 / 409	Korean	Non-segmental	rs1049623	Exon 15	NS	-	Kim et al,	2010 [62]
		C C	1392 / 2629	European	Generalized	rs2267641	Exon 17	NS	-	Birlea et al,	2011 [47]
NLRP1	17p13	B F	114 F (656 IND)*	American / European	Generalized + DAA	rs6502867	Intron 15	P< 0.001a	2.8 (1.37 - 3.15)	Jin et al,	2007 [36]
						rs4790797	#	P<0.001a	2.1 (1.39 - 2.91)		
		C C	66 / 93	Romanian	Generalized	rs6502867	Intron 15	P= 0.019b	1.86 (1.09 - 3.21)	Jin et al,	2007 [59]
						rs2670660	#	P=0.039b	1.54 (1.03 - 2.39)		
		C C	26 / 61	Arab	Generalized	rs1008588	#	P=0.027	N.A	Alkhateeb et al,	2010 [60]
						rs2670660	#	P=0.038	N.A		
PTPN22	1p13.3-p13.1	C C	165 / 304	European	Generalized	1858 C/T	Exon 14 (R620W)	P=0.005 c	1.82 (1.17 - 2.82)	Canton et al,	2005 [133]
		C C	126 / 140	Indian	Generalized	1858 C/T (R620W)	Exon 14	NS	-	Laddha et al,	2008 [134]
		C C	65 / 111	Romanian	Generalized	1858 C/T (R620W)	Exon 14	P=0.036 c	2.92 (1.21 - 7.03)	LaBerge et al,	2008 [135]
		B F	126 F (712 IND)*	American / European	Generalized + DAA	1858 C/T (R620W)	Exon 14	P=0.024 a	2.16 (1.22 - 3.82)	LaBerge et al,	2008 [136]
		C C	55 / 85	Arab	Generalized	1858 C/T (R620W)	Exon 14	NS	-	Alkhateeb et al,	2010 [60]
XBP1	22q12.1	C C	319 / 294	Chinese Han	Vitiligo per se	rs2269577	Promoter	P=0.007	1.36 (1.09 - 1.71)	Ren et al,	2009 [37]
			365 / 404	Chinese Han	Vitiligo per se	rs2269577	Promoter	P= 0.008	1.31 (1.07 - 1.59)		
			1402 / 1288	Chinese Han	Vitiligo per se	rs2269577	Promoter	P=0.003	1.18 (1.06 - 1.32)		
		C C	896 / 1515	European	Generalized	rs2269577	Promoter	P=0.00075	1.17 (1.06 - 1.29)	Birlea et al,	2011 [47]
		M A	2653 / 2980	European / Chinese		rs2269577	Promoter	P= 0.0000000095	1.21 (1.13 - 1.19)		

C C, Case-control design. B F, Family-based design. M A, Meta analysis. * F, family, (IND =individuals). DAA, Associated Autoimmune Disease. IIP, Early Age of Onset. #, Intergenic region.
[a] Conditioned logistic regression analysis. [b] Allelic association. [c] Genotypic association. NS, non-significant. NA, Not available. OR, odds ratio. CI, Confidence interval.

was *NLRP1*, located in chromosome region 17p13, which encodes an innate immune system regulatory protein. *NLRP1* gene polymorphisms were first investigated and associated to American families affected with generalized vitiligo and autoimmune diseases epidemiologically associated to vitiligo; later, the association signal was replicated in independent case-control populations from Romania and Jordan, using the generalized vitiligo phenotype. [36, 59, 60]

Successful fine mapping of 22q12 *locus* identified *XBP1* gene associated with vitiligo. *XBP1* encodes a transcription factor that regulates the expression of MHC class II genes. The identification of genetic variant rs2269577, located in *XBP1* gene promoter region associated with vitiligo *per se*, was possible due to the progressive realization of association analyzes in three independent population samples, both case-control and families. Furthermore, a functional study showed high expression of XBP1 in the injured skin of patients who carry the risk allele C of rs2269577 polymorphism.[37] Interestingly, the same risk allele of variant rs2269577 was replicated in a European population in a case-control association study. [59]

Another approach is the selection of genes involved in important biological pathways in the disease pathogenesis, as is the case with *DDR1* gene, located on chromosome region 6p21. DDR1 gene encodes a transmembrane tyrosine kinase receptor; mutations in this gene can lead to alterations in melanocyte adhesion to basal membrane via integrin CCN3. Association between DDR1 gene polymorphisms and vitiligo *per se* has been reported in a population from southern Brazil. Interestingly, the association signal observed was strongly dependent on age, suggesting a more pronounced genetic effect in patients affected with vitiligo that were aged ≤ 18 and 25.[61] It is important to note that, one study in a Korean population sample replicated the association between vitiligo and *DDR1* variants, although the statistical signal has not withstood correction for multiple testing.[62] Another independent study failed to replicate the same association; however, the authors did not evaluate the population sample stratified by age of vitiligo onset.[47] Recent functional studies have shown that the decreasing of melanocyte adhesion in the basal lamina is due in part to decreased expression of *DDR1*. [63, 64]

GENOME WIDE ASSOCIATION STUDIES - GWAS

GWAS involve hundreds of thousands of genetic markers, enough for complete genome coverage, which are tested in combination to determine their association with a particular disease. This method is free of functional or positional hypotheses, since the only goal in selecting the collection of markers to be tested is to achieve the most substantial coverage possible, including all genes in the genome that are investigated in a single experiment. Thus, GWAS allow the identification of genes previously unsuspected of participating in the pathogenesis control of the studied disease.

The first GWAS in vitiligo was conducted in a genetically isolated population sample under strong founder effect (thus presenting lower genetic variability) in northwestern Romania, with a high prevalence of generalized vitiligo, the authors found an association between the disease and SMOC2 gene marker rs13208776 (p=3.13×10^8); yet, this finding was not replicated.[65] Subsequently, two independent GWAS for generalized vitiligo, conducted in Caucasian and Chinese samples, found many signs of vitiligo associated with polymorphisms of several *loci*, including the MHC.[66, 67] Only 2 of these signals for LPP and IKZF4 genes were replicated in population samples different from the original ones. [36, 65, 67, 68]

ETIOPATHOGENESIS

The etiopathogenesis of vitiligo has not been fully elucidated and several theories have been proposed. Among those, the autoimmune hypothesis is currently the most accepted by experts.[69,70] Besides this theory, others have been intensively studied, such as epidermal adhesion defect, biochemical and neural hypotheses. This article will discuss the adhesion defect, autoimmune and biochemical theories.

AUTOIMMUNE THEORY

The initial perception that autoimmunity was involved in patients with non-segmental vitiligo was based on the frequent co-occurrence of autoimmune diseases in these patients and their relatives, such as lupus erythematosus, psoriasis, alopecia areata, halo nevi and mainly autoimmune thyroid diseases, besides the favorable response to immunosuppressive therapies such as photochemotherapy with UVA (PUVA) and topical and oral corticosteroids.[71-76] In this regard, it has been determined that therapy with systemic corticosteroids decreased antibody mediated cytotoxicity against melanocytes in patients with vitiligo.[77]

In addition, two large epidemiological studies found different prevalence rates of autoimmune comorbidities in patients with vitiligo, especially thyroid diseases, in this case, 7.7% in Chinese subjects, contrasting with a higher prevalence of 20% in Caucasians.[11,78] A recent systematic review of thyroid diseases in patients with vitiligo identified average prevalence rates of thyroid diseases, autoimmune thyroid diseases, and the presence of thyroid-specific autoantibodies, respective-

ly 15.1%, 14.3% and 20.8%, and a corresponding relative risk (RR) for those affected of 1.9, 2.5 and 5.2.[79]

Vitiligo is accompanied by abnormal humoral and cellular immunity and high levels of serum circulating autoantibodies have been detected in 5 to 10% of patients, predominantly of the IgG class and particularly anti-tyrosinase one and two (TRP-1 and TRP-2), however the role of anti-melanocyte antibodies in vitiligo pathogenesis remains uncertain and it has been suggested that their presence may be secondary to keratinocyte and melanocyte damages.[70, 80-85]

Melanocytes are capable of presenting antigens in the presence of MHC class II, which would allow HLA-DR+ cells present in the perilesional vitiligo area to present antigens in response to trauma or local inflammation, in the latter case leading to autoimmune destruction of melanocytes.[86, 87] Several studies have demonstrated the presence of CD4^{+} and CD8^{+} lymphocytic infiltrates in the dermo-epidermal junction in perilesional vitiligo skin.[87,88] It has been observed experimentally that in some patients with common vitiligo, there was infiltration of CLA[+]T cells in the perilesional skin, thus being possible that the recruitment of these T cells occurred through dendritic cells activation, and these in turn are activated at the epidermal trauma region.[89,90] Recently, data that may confirm this hypothesis were found, an immunohistochemistry study demonstrated an increased population of CD11c^{+} myeloid dendritic dermal cells and CD207^{+} Langerhans cells in the lesional border of vitiligo patches.[91]

Interestingly, melanocyte-specific cytotoxic T lymphocytes were associated with disease activity.[92] More recently, an *in vitro* study showed that cytotoxic T lymphocytes infiltrated in common vitiligo perilesional area destroyed neighboring melanocytes.[93]

Melanocytes and melanoma cells share differentiation antigens, and based on the number of cases observed in humans and mice, the spontaneous development of vitiligo in patients with melanoma has been considered as a sign of good prognosis for this tumor.[94-96] In this regard, various studies about vitiligo's immunology are derived from the study of melanoma and melanoma vaccines; for example, immunotherapy against antigens such as gp100 and tyrosinase may lead to cytotoxic T lymphocytes infiltration both in the specific melanoma area as in vitiligo lesions.[97-99]

Mice with surgically excised melanoma tumors generated cytotoxic T lymphocyte memory response against melanocytes, these mice that lacked regulatory T cells (TREGs) developed vitiligo, suggesting that TREGs would prevent autoimmunity against melanocytes.[100] New data on patients with vitiligo corroborate these results, with the detection of reduced levels of chemokine CCL22, which increases TREGs (*Regulatory T cells*) migration toward the injured skin, leading to an inadequate number of TREGs in patients with vitiligo, insufficient to suppress a cytotoxic reaction in the skin of affected individuals.[101] In this same line of research, flow cytometry analysis revealed an increase in circulating CD8^{+} and a decrease in TREGs in patients with generalized vitiligo, in addition, expressive increases in these two cell types were identified in the perilesional skin of patients. However, regulatory T cells from peripheral blood had decreased ability of suppressing CD8^{+} T lymphocytes, suggesting that TREGs' malfunction and an increase in lymphocytes contributed to the destruction of melanocytes in the affected individuals.[102] In contrast with some results of the latter article, another study did not find increase in TREGs or CD8^{+} T lymphocytes in the peripheral blood of patients with generalized vitiligo compared with controls, however, these cells were not assessed in vitiligo perilesional skin areas in this particular study.[103] Nevertheless, a relevant fact detected in by the authors was the decrease of invariant natural killer T cells (*i* NKT) in peripheral blood, these are regulatory cells, responsible for the Th1/Th2 immune response balance that are often diminished in other autoimmune diseases such as lupus erythematosus and rheumatoid arthritis, suggesting a protective effect on their part.[103]

The mechanism of self-tolerance loss, which magnifies the autoreactive cytotoxic lymphocytes actions in the destruction of melanocytes, is still unknown; a recent study showed evidence of functional defects in peripheral regulatory T cells (TREGs) in half of the patients tested with unstable vitiligo.[104]

It has also been found in segmental vitiligo, whose pathogenesis was primarily linked to sympathetic nerves dysfunction, evidence that immune-mediated cellular responses including CD8^{+} T lymphocytes is involved in the early stages of this type of disease, moreover, in the same study flow cytometry detected a high expression level of IFN-γ in injured skin.[105]

A profile of Th-1 cytokines, Interferon-g, TNF-a and recently IL-8, has been well described in vitiligo skin areas both segmental and non-segmental.[105-109] Besides Th-1 response, many evidences of Th-17 influence have been reported in vitiligo, with IL17^{+} lymphocytes infiltration in dermal areas on the border of vitiligo lesions being demonstrated by immunohistochemistry and immunofluorescence; in addition, an increased expression of IL-17A and IL-1 b was also found on the edges of lesions.[91] An increase of IL-17 in the serum of patients affected by vitiligo was recently described.[110]

ADHESION DEFECT THEORY

It has been suggested that adhesion defects are involved in the disappearance of melanocytes in vitiligo lesions.[63] The main clinical sign reinforcing this theory is the occurrence of koebnerization or Köebner phenomenon (appearance of vitiligo after an acute or chronic trauma), which may be present in up to 31% of Caucasian patients with common vitiligo.[111]

In one of the earliest studies that attempted to identify adhesion defects in the genesis of vitiligo, an immunohistochemical analysis was performed and demonstrated that tenascin protein, which can interfere with melanocyte adhesion, was over-expressed in damaged skin compared to the healthy skin of the same patients.[112, 113]

Experimental study with patients of the generalized subgroup (which included common, acrofacial and universal types) demonstrated that these patients presented melanocyte detachment after mechanical rubbing of the unaffected skin.[114] This observation led to the proposal of a new theory that non-segmental vitiligo is a melanocytorrhagic primary disorder, i.e., there would probably occur an acute loss of melanocytes (because most patients have a sudden onset of lesions), with an altered response of melanocytes to friction and possibly other types of stress, which would induce cell detachment and subsequent transepidermal loss. In this context, the authors of this theory speculated that an autoimmune phenomenon might be triggered by antigen release and recognition of affected melanocytes by dendritic cells or memory T cells during trans-epidermal migration, thereby exacerbating the detachment and loss of more melanocytes.[30]

Alterations in the main protein that adheres melanocytes to the epidermis basal layer, DDR1 (Discoidin Domain Receptor-1) have been implicated as one of the aggravating factors in the loss of melanocytes. Initially, genetic association studies have found evidence of a connection between non-segmental vitiligo and DDR1 gene alleles, which was more evident in vitiligo patients with the onset of disease before 25 years of age.[61, 62]

Functional studies attempting to explain the involvement of DDR1 and CCN3 protein (which controls the adhesion of DDR1 to epidermis basal layer [115,] observed that perilesional melanocytes did not express CCN3, moreover, the silencing of CCN3 in melanocytes induced a significant inhibition of their adhesion to collagen IV.[63] In this same study, it was demonstrated that the expression of DDR1 in lesional skin was decreased compared to perilesional skin in most patients, and collagen IV expression was diminished in all affected individuals.[63] In this same research

line, a recent study confirmed the decreased expression of DDR1 in all lesional epidermis, whereas epidermal expression of DDR1 was secondary only to expression in keratinocytes and not in epidermis basal layer, where melanocytes are located. This study hypothesized that the vitiligo is a condition in which all the epidermis is affected and not only melanocytes. [64]

VITILIGO'S BIOCHEMICAL THEORY

The hypothesis that vitiligo could be caused by a metabolic pathway dysfunction, not necessarily related to melanocytes, which would lead to the production of toxic metabolites such as catecholamines, *o*-quinones and reactive oxygen species, has been widely investigated.[31,70]

The involvement of oxidative stress damage to melanocytes is supported by evidence suggesting an imbalance between the oxidant/antioxidant systems in the epidermis of patients with vitiligo. It has been demonstrated that melanocytes on the lesion borders of vitiligo patients showed increased sensitivity to oxidative stress when in culture.[116] Schallreuter et al. observed *in vivo* that patients with vitiligo can accumulate a concentration of H_2O_2 over 10^{-3} M in their epidermis.[117] Different possible sources of endogenous production of H_2O_2 in the epidermis of vitiligo patients have been described, including an increase in monoamine oxidase A (MAO-A), increased activity of NADPH-oxidase and imbalance in (6R)-L-erythro 5,6,7,8-tetrahydrobiopterin (6-BH4) synthesis/recycling/regulation.[117-120] One of the likely consequences of increased 6-BH4 production observed in the epidermis of affected patients is the inhibition of phenylalanine hydroxylase enzyme, responsible for producing L-tyrosine from L-phenylalanine, leading to low levels of tyrosine and therefore, a defect in melanin synthesis.[121]

Patients with vitiligo have a low level/activity of enzymatic and non-enzymatic antioxidants such as catalase, glutathione peroxidase and vitamin E, possibly increasing H_2O_2 toxicity.[122-124] The results obtained for the levels of superoxide dismutase antioxidant were conflicting amongst studies.[122,123,125,126] Further evidence on the involvement of oxidative stress in the disease pathogenesis is the suspension of the depigmentation process and skin color recovering with the removal of epidermal H_2O_2 by Narrow-Band-UVB 311nm activated pseudocatalase.[117]

Studies have reported the involvement of the adrenergic and cholinergic systems in vitiligo pathogenesis.[127] Acetylcholinesterase (AChE) is an important enzyme in promoting and maintaining oxidative stress, being inactivated by oxidation of Trp,[432] Trp,[435] Met[436] residues by H_2O_2. Interestingly, AChE activity

is low in vitiligo skin lesions during depigmentation, but it returns to normal when the damaged skin starts repigmentation.[128] Picardo et al. showed that abnormal catecholamine release by autonomic nerve terminations could result in excessive production of toxic radicals in the melanocyte microenvironment.[125] Furthermore, high levels of catecholamine metabolites in the urine of patients with vitiligo during the active phase of disease have been reported, when compared with age-matched controls.[129,130] ❏

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