

## Vitiligo: current medical and scientific understanding

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**Vitiligo is a relatively common acquired skin depigmentary disease with a complex presentation, therapy, and etiology. Both the prognosis and therapeutic response for patients with vitiligo is unpredictable. Multiple current therapies exist however the efficacy of these are not optimal. The cause of vitiligo appears to be a combination of genetic effects in both the immune system and the melanocyte itself with a precipitating factor instigating their interaction and resulting in the melanocyte destruction. Headway is being made in understanding the etiology of vitiligo that should culminate in new and improved therapies.**

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**V**itiligo is a common disorder but its causes and aggravating factors remain mysterious and puzzling. The earliest descriptions of vitiligo date back thousands of years. Fortunately, knowledge of its etiology has improved in the past few years.

Vitiligo is an acquired depigmentary disease in which white macules appear on the skin.<sup>1, 2</sup> Vitiligo can begin at almost any age, the earliest age noted in a child of 6 months and the oldest individuals in their 70's. Lesions can begin anywhere on the skin. However, more frequently they initially appear around the mouth, the eyes, on the fingers, wrist, and over the elbows and knees (termed acrofacial vitiligo); areas with the most physical microtrauma. Prognosis and progression of bilateral (acrofacial) vitiligo are not predictable. There are self limiting forms of vitiligo,

*i.e.*, segmental Vitiligo, which has a limited course. Lesions may remain as a small discrete spot(s) for month or years or they may rapidly enlarge, spread and coalesce with new lesions frequently appearing. A Wood's lamp (400 nm) examination is helpful in identifying and locating depigmentation in individuals with fair skin.

The classification of vitiligo has recently been revised. Originally the classification had a number of categories, *i.e.*, generalized, focal, acrofacial, total, inflammatory, contact/occupational and unilateral (segmental).<sup>3</sup> Some of these, *i.e.*, acrofacial, generalized and total, probably are phases of the same disorder. More recently it was recommended that vitiligo be classified into two forms: Vitiligo vulgaris/non-segmental vitiligo (NSV) and segmental vitiligo (SV).<sup>4</sup> Bilateral or non segmental vitiligo presents with white patches on both sides of the body, remarkably symmetrical. SV is unilateral and affects only one side of the body. It affects a segment of

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the integument. The patches do not follow any currently known embryological distribution such as dermatomes, metameres or the distribution of the autonomic nervous system. However, the patterns of segmental vitiligo are not random and different individuals will exhibit similar patterns of pigment loss. This observation suggests that there is some biologically important determinant of the distribution of pigment loss. It might be that they represent melanocyte embryological migration patterns.

Although the prevalence of vitiligo around the globe is relatively uniform, there are several isolated areas where vitiligo seems more or less prevalent. These would be, or have been, good populations to study genetically for possible clue to the promotion or suppression of this disease, respectively. The usual prevalence worldwide ranges from 0.5-1.0% affecting equally both genders and individuals of all racial backgrounds. In the Surat area of western India<sup>5</sup> and in the mountains of northern Romania<sup>6</sup> the incidence of vitiligo is 3.6% and 2.9%, respectively. In contrast, the incidence of vitiligo in the Isle of Bornholm in Denmark is relatively rare with a reported incidence of 0.38%.<sup>7</sup>

Vitiligo is a disorder that destroys melanocytes. There are melanocytes in parts of the body other than the skin, for example in the eyes, the ears and leptomeninges. Focal areas of depigmentation in the iris, anterior chamber, and the retinal pigmented epithelium associated with uveitis have been observed in patients with vitiligo.<sup>8,9</sup> Although most patients with vitiligo have no ocular symptoms from these lesions, some complain of photophobia and night blindness. Both the ear (predominantly the stria vascularis)<sup>10</sup> and the leptomeninges covering the pons area in the brain stem<sup>11</sup> contain melanocytes. Studies have confirmed that these organs also can exhibit damage to melanocytes. It has been reported that some individuals with vitiligo have dysacusia and headaches. Damage to melanocytes in the stria vascularis of the inner ear or in the leptomeninges could produce these symptoms and signs.<sup>12,13</sup>

Some autoimmune based systemic disorders occur in the vitiligo population at a prevalence that exceeds that of the general public. Autoimmune thyroiditis affects 15% of those with vitiligo. Other disorders such as pernicious anemia, Addison's disease, lupus erythematosus, rheumatoid arthritis, diabetes<sup>14</sup> have a higher incidence in people with vitiligo. These diseases can occur with higher prevalence in family

members without vitiligo. This is consistent with the recent demonstration that candidate genes associated with vitiligo can affect the autoimmune response to a variety of tissues (see below).

Vitiligo is a biological disorder that disfigures the individual but can have significant psychological, social and sexual ramifications. A few vitiligo patients become severely depressed to the point of being reclusive.<sup>15</sup> In a study of a population of patients with vitiligo it was demonstrated that 7% exhibited severe depression, 32% with acute and/or consistent embarrassment, 27% with mild embarrassment. About 33% showed no social effects or embarrassment from the disfigurement of depigmentation.<sup>16</sup> Using the Arizona Sexual Experience Scale (ASEX), researchers have demonstrated that vitiligo results in reduced sex drive, arousal, maintenance, and satisfaction.<sup>17</sup> In general, patients with vitiligo assessed by the Dermatology Life Quality Index (DLQI) exhibit a lower quality of life than normal subjects or even patients with psoriasis.<sup>18</sup>

### Therapy

Ideally the goal to therapy for vitiligo is two-fold; to halt the progression of depigmentation by suppressing the immune response and to induce repigmentation by encouraging melanocytes in pigmented hair follicles of the lesion to migrate out and repopulate the interfollicular epidermis. Unfortunately, current therapies fail often in both respects. There is no known method to halt the spread of vitiligo or prevent its recurrence at some time in the future. The holy grail of vitiligo research is to find such a medication. Were it possible to stop the process of melanocyte destruction, the problem of vitiligo would be mostly solved. The initial modality for therapy is topical application of steroids and/or immunomodulators such as Protopic and Elidel for 3 to six months. Results of recent clinical studies have demonstrated ~50% success rate with these topical agents.<sup>19</sup> Other topical agents with some success include topical vitamin D preparations (Dovonex®). The use of these agents usually is combined with phototherapy of some form.

Originally, PUVA (psoralen + ultraviolet A) was the phototherapy of choice. However, prolonged use of PUVA in a patient population with psoriasis caused a high incidence of both non melanoma and

melanoma skin cancer decades later.<sup>20</sup> PUVA has fallen out of use. Narrow Band UVB (310-314 nm) with or without the concurrent uses of topical medications has been most promising to repigment white skin.<sup>21</sup> Excimer laser (309 nm) is a form of narrow band UV and has been useful for treating small discrete spots of depigmentation.<sup>21</sup>

Vitiligo can be repigmented if the disorder is stable, *i.e.*, not progressing, and if the white spots have pigmented hairs. Melanocytes within hair follicles are the reservoir for repigmentation. They can be induced to proliferate within the follicle and migrate into the interfollicular skin thereby repigmenting the white skin. Glabrous skin (that is devoid of hair follicles), such as on the finger tips, the feet, ventral wrist, the genitalia, cannot respond to medical treatment such as topical steroids and light. There is no reservoir. Likewise hair bearing skin that has white hairs cannot respond to medical therapies.

The melanocyte reservoir can be replaced surgically in some patients. The best patient candidates are those with segmental vitiligo. Segmental vitiligo typically spreads within its area for a period of one to two years and then stops. The remainder of the integument is not affected. These patients make excellent candidates for surgical treatments because their disorder is inactive and does not affect or Koebnerize into the normal skin. Some patients with bilateral vitiligo whose disease is stable for at least 2 years also can be transplanted successfully.

Various procedures have been utilized in this method including blister grafting, punch biopsy grafting, epidermal slur grafting, and cultured melanocyte transplantation.<sup>22</sup> Unfortunately, surgical procedures are not readily available and only a few centers capable of performing these transplants. The procedures are costly and not covered by insurance.

Some individuals have extensive vitiligo, particularly on the exposed skin of the face, neck, arms, and hands. Often the depigmentation covers more than 50% of the skin of these areas. A therapeutic choice for a patient with extensive, nonresponsive vitiligo is depigmentation therapy.<sup>23</sup> Monobenzyl ether of hydroquinone is an agent that can remove pigment from normal skin. The procedure is easy, application of the medication daily. However it takes a long time to accomplish complete depigmentation, up to a year or more. In addition, the completeness and permanency of the resulting depigmentation cannot be guaranteed.

## Etiology

The cause of vitiligo is still unknown. It seems to require three factors: 1) a complex of vitiligo susceptibility genes that influence the autoimmune response; 2) genetically abnormal melanocytes; 3) an environmental or physiological factor(s) that activates the genetic program for melanocyte destruction.<sup>24</sup> The current dogma is that there are several genes affecting the immune system and the pigment system that predispositions someone to developing vitiligo. However, a precipitating factor must illicit the interaction between the immune system and the melanocyte resulting in the destruction of the melanocyte population in discrete areas of the skin.

It is clear that the melanocyte population in the white epidermis has been depleted. Accompanying this removal can be a subtle appearance of immunocytes in these lesions, particularly at the border between the white and normal appearing skin.<sup>25</sup> The presence of inflammatory cells at the border of a vitiligo lesion can become very marked, particularly in inflammatory vitiligo which is manifested by red, edematous and itchy skin. When present, these inflammatory cells are predominantly CD4+ and CD8+ T-cells<sup>26, 27</sup> that can express the skin homing CLA marker.<sup>28</sup> In addition, CD11+ dendritic cells, putative capable of antigen presentation, have been identified in close proximity to melanocytes in perilesional skin.<sup>29</sup> Functionally, T-cells isolated from vitiligo lesions can demonstrate melanocyte specific cytotoxic in non-lesional skin.<sup>30</sup> However, in a significant number of lesions immunocytes may not be detectable, especially when in lesions that are dormant.

There is additional evidence for a melanocyte specific autoimmune response mediating melanocyte removal in vitiligo. Immunotherapy for metastatic melanoma utilizes melanocyte specific T-cells to destroy the malignant melanocytes. Tumors at times regress and some patients develop depigmentation of normal appearing skin.<sup>31</sup> The depigmentation resembles vitiligo although it is not known if the mechanism of destruction is identical to or similar to that which occurs in vitiligo. In one publication, a melanoma patient treated with CD8+ T-cell clone that was reactive for MelanA/MART-1 developed multiple depigmented lesions,<sup>32</sup> demonstrating that cytotoxic CD8+ cells against melanocyte differentiation antigens can cause melanocyte destruction that results in depigmentation.

The humoral immune system also has been implicated in the etiology of vitiligo. Serum autoantibodies against many melanocyte cytoplasmic antigens have been identified in vitiligo patients.<sup>33</sup> Serum from patients with vitiligo can cause antibody dependent cellular cytotoxicity as well as complement dependent cytotoxicity of cultured melanocytes.<sup>34,35</sup> However, the cytotoxicity is not specific for melanocytes. In addition, injection of the IgG fraction of serum from patients with vitiligo into human skin grafted on nude mice results in melanocyte destruction in the graft.<sup>36</sup> Histological evidence of B cells or immunoglobulin deposits in the epidermis of advancing lesions of vitiligo has not been demonstrated.<sup>37,38</sup> It is yet to be confirmed whether these melanocyte specific antibodies play a direct or indirect role in the etiology of vitiligo.

Genetic analysis of vitiligo, specifically with the use of genome-wide linkage and association studies, is beginning to provide information about the genes that are associated with vitiligo.<sup>39</sup> Several recent genes identified as candidates in the etiology of vitiligo have effects on the immune response and are involved in the cause of other autoimmunity disorders. One locus at chromosome 1p31.3-32.2 (labeled as an autoimmunity susceptibility locus – AIS1) contains multiple genes. Single nucleotide polymorphisms in one of these candidate genes (FOXD3) co-segregated with vitiligo in the study of a single family.<sup>40</sup> FOXD3 encodes a forkhead transcription factor that is a primary regulator of melanoblast differentiation in the embryonic neural crest.<sup>41</sup> However, other vitiligo patients do not appear to have mutations of FOXD3, and other families do not show linkage to the AIS1 region of chromosome 1p<sup>42</sup> suggesting that this mutation may be a unique isolate.

A second candidate gene is NALP1 on chromosome 17p13.<sup>43,44</sup> This gene was first identified by Nath *et al.*<sup>45</sup> who noted it is associated both with vitiligo and lupus erythematosus. This gene was later found to interact with loci on Chromosomes 7 and 9.<sup>46</sup> This is a very interesting gene because the NALP1 protein is a component of the inflammasome, a cytoplasmic multiprotein complex that regulates the innate immune system, mediate the maturation of proinflammatory cytokines like interleukin-1 $\beta$  and -18, and stimulates cellular apoptosis.<sup>47</sup> This gene and its activities could be involved in causing melanocyte destruction and thereby vitiligo.

Recently, significant associations between gen-

eralized vitiligo and SNPs at several other loci previously associated with other autoimmune disease have been detected.<sup>48</sup> The strongly associated SNPs were distributed across the major-histocompatibility-complex loci on Chromosome 6p21.3 between several MHC class I and class II encoding area. In addition, it has recently been reported that variants in PTPN22,<sup>49,50</sup> that putatively functions as a general autoimmunity susceptibility loci, and SMOC2,<sup>51</sup> of unknown function, may also be associated with the risk of vitiligo.

In addition to a genetic aberration in the immune system, the etiology of vitiligo appears to also have a genetic defect in the melanocyte itself. Prior studies have demonstrated that the melanocytes in the skin of vitiligo patients can exhibit morphologic abnormalities including enlargement, fragmentation, Extracellular Granular Material (EGM) and dilated RER.<sup>52</sup> Several other studies have demonstrated that the melanocyte from vitiligo skin appears fragile. The inability to culture melanocytes from pigmented skin of vitiligo patients using routine procedures and the fragility of established cultures of melanocytes has been demonstrated.<sup>53</sup> The most suggestive evidence that vitiligo melanocytes possess a genetic aberration was demonstrated by a study where an isoform of tyrosinase was also identified to correlate with vitiligo by a genomewide association study.<sup>48</sup> A more recent study assessed single nucleotide polymorphisms for genes encoding enzymes involved in melanin synthesis in patients with vitiligo and found evidence for association of tyrosinase and DOPAchrome tautomerase with vitiligo susceptibility.<sup>54</sup> These studies confirm that long held theory that an innate defect in vitiligo melanocytes exists.

Despite the fact that genetic alterations in the immune system and the melanocyte may exist in vitiligo, a precipitating factor must be at the basis of instigating melanocyte destruction in this post-natal acquired disease. The concordance of vitiligo in monozygotic twins is only 23%, indicating that a non-genetic component also plays an important role in vitiligo.<sup>55</sup> Anecdotal correlations of personal events with the onset with vitiligo also imply the existence of a precipitating factor. These events include severe sunburn, pregnancy, physical and emotional stress/trauma, wounds or areas of microtrauma, etc. Contact/occupational vitiligo is the most obvious form of the disease that correlates a precipitating factor (primarily phenolic and catecholic deriva-

tives) with the onset of melanocyte destruction.<sup>56, 57</sup> What most of these putative precipitating factors have in common is that they facilitate facultative pigmentation of the skin. Melanocyte-stimulating-hormone induced by UV over-exposure,<sup>58</sup> estrogens upregulated during pregnancy,<sup>59, 60</sup> cytokines produced during emotional stress and/or physical trauma (*i.e.*, nerve growth factor, neurotrophins, ACTH, endorphins, etc.),<sup>61-65</sup> and cytokines released during wound healing particularly at sites of microtrauma<sup>66</sup> can all trigger facultative melanin synthesis by melanocytes. Therefore, enhanced facultative melanization could put undue intolerable stress on the vitiligo melanocyte resulting from an elevation in cytotoxic oxidative melanin intermediates. Consistent with this is the correlation of a tyrosinase isoform with vitiligo as described above.<sup>48</sup> This isoform of tyrosinase could allow the melanocyte to present a melanocyte specific autoantigen to the primed hyper-reactive immune system inducing autoimmunity. Alternatively, transcription and/or maintenance of this isoform of tyrosinase may render the melanocyte to be hyper-reactive to facultative stimulators of melanization and consequently increase pigment production beyond the threshold tolerated by the vitiligo melanocytes.

How can the various precipitating factors initiate the interplay between the sensitive vitiligo melanocytes and the attuned autoimmune response leading to melanocyte removal? The induction and/or combating of oxidative stress have been implicated by numerous studies.<sup>67</sup> Disruption on the bipterin metabolic pathway and network can induce H<sub>2</sub>O<sub>2</sub> generation or impede its neutralization.<sup>68, 69</sup> Generation of reactive oxygen species is hazardous to the cells initially causing lipid peroxidation, etc.<sup>70</sup> and ultimately inducing apoptosis.<sup>71</sup> It has recently been demonstrated that vitiligo melanocytes exhibit 1) more reactive oxygen species; 2) membrane peroxidation; 3) impaired mitochondrial electron transport chain 1; and 4) more readily induced apoptosis, all characteristics of cells susceptible to death by oxidative stress.<sup>72</sup> It has been demonstrated by several independent studies that the antioxidant catalase, and putatively the ability to combat oxidative stress, appears to be genetically impaired in some patients with vitiligo. Specifically, 1) levels of catalase in the epidermis of some patients with vitiligo are reduced,<sup>73</sup> 2) a variant genotype of catalase (C>T SNP in codon 419 of exon 10) has been associated with

susceptibility to vitiligo,<sup>74</sup> and 3) a promoter variant of the *Catalase* gene (-89A>T) correlates with susceptibility to vitiligo in the Chinese population.<sup>75</sup> Many alternative cellular abnormalities have also been suggested to occur in vitiligo melanocytes such as lipid alterations in the mitochondria,<sup>76</sup> impairment in the survival/apoptosis regulation for cell survival,<sup>77</sup> inability to be stably attached to the basement membrane.<sup>78</sup> However, a common cellular/molecular denominator among these possible inherent defects has yet to be identified. It is possible that multiple and distinct genetically determined inherent defects can perturb the melanocytes and promote apoptosis may occur throughout the vitiligo syndrome. Regardless, cells that dysfunction and head towards apoptosis have been demonstrated to induce a consequential autoimmune response that perpetuates the disease.<sup>79</sup>

In summary, recent advances have been made in the classification of vitiligo and in understanding the etiology. The initial presentation and subsequent prognosis of vitiligo is extremely variable. However, vitiligo is now being classified into two subtypes, non-segmental vitiligo (NSV) and segmental vitiligo (SV). Many state-of-the-art therapies have been developed for vitiligo including more precise phototherapies and grafting surgeries. However, the efficacy of these current therapies is still very disappointing. The cause of vitiligo is more clearly being deciphered. Genes that influence the autoimmune component of the immune system as well as the function of the melanocyte have demonstrated polymorphisms and/or mutations that associate with the development of vitiligo. Precise identification of the functions of these genes and gene products, and how the autoimmune and melanocyte systems interact in the etiology of vitiligo is on the horizon. However, these genes appear to orchestrate the susceptibility for developing vitiligo in response to a precipitating factor. The identity of these various specific precipitating factors and the resulting pathophysiology should provide clues to the development of novel and more effective therapies. Most important, identification of the genes involved and the mechanisms to activate or inactivate them will provide a means to develop a medication that will halt the progression of melanocyte destruction and the subsequent depigmentation. When such a medication is available, the problem of vitiligo will mostly be solved.

## Riassunto

### *Vitiligine: attuali conoscenze mediche e scientifiche*

La vitiligine è una patologia cutanea depigmentante acquisita relativamente frequente con una presentazione, terapia ed etiologia complesse. Sia la prognosi che la risposta terapeutica del singolo paziente affetto da vitiligine non sono prevedibili. Attualmente, esistono numerose terapie, la cui efficacia tuttavia non è ottimale. La causa della vitiligine sembrerebbe essere una combinazione di effetti genetici sia nel sistema immunitario che nei melanociti con un fattore precipitante che scatenerrebbe l'interazione tra i due tipi cellulari e la distruzione dei melanociti. Si stanno attualmente facendo progressi nella comprensione dell'etiologia della vitiligine che dovrebbero portare a nuove e migliori terapie.

PAROLE CHIAVE: Vitiligo, eziologia - Prognosi - Trattamento.

## References

- Hann S-K, Nordlund JJ, eds. Vitiligo: A Monograph on the Basic and Clinical Science, 1st edn. Oxford, London: Blackwell Science Ltd; 2000.
- Picardo M, Taieb A, eds. Vitiligo. Berlin Heidelberg: Springer-Verlag; 2010.
- Hann SK, Nordlund JJ. Clinical features of generalized vitiligo. In: Hann SK, Nordlund JJ, Eds, Vitiligo: A Monograph on the Basic and Clinical Science. Oxford: Blackwell Scientific; 2000. p. 35-48.
- Taieb A, Picardo M. Epidemiology, definitions and classification. In: Picardo M, Taieb A, Eds, Vitiligo. Berlin Heidelberg: Springer-Verlag; 2010. p. 13-24.
- Mehta NR, Shah KC, Theodore C, Vyas VP, Patel AB. Epidemiological study of vitiligo in Surat area, South Gujarat. Indian J Med Res 1973;61:145-54.
- Birlea SA, Fain PR, Spritz RA. A Romanian population isolate with high frequency of vitiligo and associated autoimmune diseases. Arch Dermatol 2008;144:310-6.
- Howitz J, Brodthagen H, Schwartz M, Thomsen K. Prevalence of vitiligo: Epidemiological survey on the Isle of Bornholm, Denmark. Arch Dermatol 1977;113:47-52.
- Albert DM, Nordlund JJ, Lerner AB. Ocular abnormalities occurring with vitiligo. Ophthalmology 1979;86:1145-58.
- Bulbul Baskan E, Baykara M, Ercan I, Tunali S, Yucel A. Vitiligo and ocular findings: a study on possible associations. J Eur Acad Dermatol Venereol 2006;20:829-33.
- Meyer zum Gottesberge AM. Physiology and pathophysiology of inner ear melanin. Pigment Cell Res 1988;1:238-49.
- Goldgeier MH, Klein LE, Klein-Angerer S, Moellmann G, Nordlund JJ. The distribution of melanocytes in the leptomeninges of the human brain. J Invest Dermatol 1984;82:235-8.
- Boissy RE. Non-skin melanocytes in vitiligo. In: Picardo M, Taieb A, editors. Vitiligo. Berlin Heidelberg: Springer-Verlag; 2010. p. 73-8.
- Hong CK, Lee MH, Jeong KH, Cha CI, Yeo SG. Clinical analysis of hearing levels in vitiligo patients. Eur J Dermatol 2009;19:50-6.
- Mollet I, Van Geel N, Lambert J. Autoimmune/inflammatory and other diseases associated with vitiligo. In: Picardo M, Taieb A, editors. Vitiligo. Berlin Heidelberg: Springer-Verlag; 2010. p. 79-90.
- Parsad D. Quality of life. In: Picardo M, Taieb A, editors. Vitiligo. Berlin Heidelberg: Springer-Verlag; 2010. p. 135-8.
- Porter JR, Beuf AH, Lerner A, Nordlund J. Psychosocial effect of vitiligo: a comparison of vitiligo patients with "normal" control subjects, with psoriasis patients, and with patients with other pigmentary disorders. J Am Acad Dermatol 1986;15:220-4.
- Sukan M, Maner F. The problems in sexual functions of vitiligo and chronic urticaria patients. J Sex Marital Ther 2007;33:55-64.
- Ongenaes K, Van Geel N, De Schepper S, Naeyaert JM. Effect of vitiligo on self-reported health-related quality of life. Br J Dermatol 2005;152:1165-72.
- Hossani-Madani AR, Halder RM. Topical treatment and combination approaches for vitiligo: new insights, new developments. G Ital Dermatol Venereol 2010;145:57-78.
- Patel RV, Clark LN, Leibold M, Weinberg JM. Treatments for psoriasis and the risk of malignancy. J Am Acad Dermatol 2009;60:1001-17.
- Nicolaidou E, Antoniou C, Stratigos A, Katsambas AD. Narrow-band ultraviolet B phototherapy and 308-nm excimer laser in the treatment of vitiligo: a review. J Am Acad Dermatol 2009;60:470-7.
- Holla AP, Parsad D. Vitiligo surgery: its evolution as a definite treatment in the stable vitiligo. G Ital Dermatol Venereol 2010;145:79-88.
- Picardo M, Dell'Anna ML. Depigmenting agents. In: Picardo M, Taieb A, Eds, Vitiligo. Berlin Heidelberg: Springer-Verlag; 2010. p. 439-42.
- Boissy RE, Spritz RA. Frontiers and controversies in the pathobiology of vitiligo: separating the wheat from the chaff. Exp Dermatol 2009;18:583-5.
- Hann SK, Park YK, Lee KG, Choi EH, Im S. Epidermal changes in active vitiligo. J Dermatol 1992;19:217-22.
- Le Poole IC, van den Wijngaard RMJG, Westerhof W, Das PK. Presence of T cells and macrophages in inflammatory vitiligo skin parallels melanocyte disappearance. Am J Pathol 1996;148:1219-28.
- Tu CX, Gu JS, Lin XR. Increased interleukin-6 and granulocyte-macrophage colony stimulating factor levels in the sera of patients with non-segmental vitiligo. J Dermatol Sci 2003;31:73-8.
- van den Wijngaard R, Wankowicz-Kalinska A, Le Poole C, Tigges B, Westerhof W, Das P. Local immune response in skin of generalized vitiligo patients. Destruction of melanocytes is associated with the prominent presence of CLA+ T cells at the perilesional site. Lab Invest 2000;80:1299-309.
- Kroll TM, Bommasamy H, Boissy RE, Nickoloff BJ, Mestrlil R, Le Poole IC. 4-Tertiary butyl phenol exposure sensitizes melanocytes to dendritic cell mediated killing. J Invest Dermatol 2005;124:798-806.
- van den Boorn JG, Konijnenberg D, Dellemijn TA, van der Veen JP, Bos JD, Melief CJ *et al.* Autoimmune destruction of skin melanocytes by perilesional T cells from vitiligo patients. J Invest Dermatol 2009;129:2220-32.
- Luiten RM, Kueter EW, Mooi W, Gallee MP, Rankin EM, Gerritsen WR *et al.* Immunogenicity, including vitiligo, and feasibility of vaccination with autologous GM-CSF-transduced tumor cells in metastatic melanoma patients. J Clin Oncol 2005;23:8978-91.
- Yee C, Thompson JA, Roche P, Byrd DR, Lee PP, Piepkorn M *et al.* Melanocyte destruction after antigen-specific immunotherapy of melanoma: direct evidence of t cell-mediated vitiligo. J Exp Med 2000;192:1637-44.
- Kemp EH, Gavalas NG, Gawkrödger DJ, Weetman AP. Autoantibody responses to melanocytes in the depigmenting skin disease vitiligo. Autoimmun Rev 2007;6:138-42.
- Cui J, Arita Y, Bystry J. Cytolytic antibodies to melanocytes in vitiligo. J Invest Dermatol 1993;100:812-5.
- Norris DA, Kissinger GM, Naughton GM, Bystry J-C. Evidence for immunologic mechanisms in human vitiligo: Patients' sera induce damage to human melanocytes in vitro by complement-mediated damage and antibody-dependent cellular cytotoxicity. J Invest Dermatol 1988;90:783-9.
- Gilhar A, Zelickson B, Ulman Y, Etzioni A. *In vivo* destruction of

- melanocytes by the IgG fraction of serum from patients with vitiligo. *J Invest Dermatol* 1995;105:683-6.
37. Hertz KC, Gazze LA, Kirkpatrick CH, Katz SI. Autoimmune vitiligo: detection of antibodies to melanin-producing cells. *N Engl J Med* 1977;297:634-7.
  38. Bleehe SS. Histology of vitiligo. In: Klaus SN, editor. *Pigment cell 5: Part II of Proceedings of the Xth International Pigment Cell Conference*, Cambridge, Massachusetts, 1977. Basel/New York: S. Karger; 1979. p. 54-61.
  39. Spritz RA. Shared genetic relationships underlying generalized vitiligo and autoimmune thyroid disease. *Thyroid* 2010;20:745-54.
  40. Alkhateeb A, Fain PR, Spritz RA. Candidate functional promoter variant in the FOXD3 melanoblast developmental regulator gene in autosomal dominant vitiligo. *J Invest Dermatol* 2005;125:388-91.
  41. Kos R, Reedy MV, Johnson RL, Erickson CA. The winged-helix transcription factor FoxD3 is important for establishing the neural crest lineage and repressing melanogenesis in avian embryos. *Development* 2001;128:1467-79.
  42. Spritz RA. Genetics. In: Picardo M, Taieb A, editors. *Vitiligo*. Berlin Heidelberg: Springer-Verlag; 2010. p. 155-64.
  43. Jin Y, Birlea SA, Fain PR, Spritz RA. Genetic variations in NALP1 are associated with generalized vitiligo in a Romanian population. *J Invest Dermatol* 2007;127:2558-62.
  44. Jin Y, Mailloux CM, Gowan K, Riccardi SL, LaBerge G, Bennett DC *et al*. NALP1 in vitiligo-associated multiple autoimmune disease. *N Engl J Med* 2007;356:1216-25.
  45. Nath SK, Kelly JA, Namjou B, Lam T, Bruner GR, Scofield RH *et al*. Evidence for a susceptibility gene, SLEV1, on chromosome 17p13 in families with vitiligo-related systemic lupus erythematosus. *Am J Hum Genet* 2001;69:1401-6.
  46. Jin Y, Riccardi SL, Gowan K, Fain PR, Spritz RA. Fine-mapping of vitiligo susceptibility loci on chromosomes 7 and 9 and interactions with NLRP1 (NALP1). *J Invest Dermatol* 2010;130:774-83.
  47. Martinon F, Gaide O, Petrilli V, Mayor A, Tschopp J. NALP inflammasomes: a central role in innate immunity. *Semin Immunopathol* 2007;29:213-29.
  48. Jin Y, Birlea SA, Fain PR, Gowan K, Riccardi SL, Holland PJ *et al*. Variant of TYR and autoimmunity susceptibility loci in generalized vitiligo. *N Engl J Med* 2010;362:1686-97.
  49. LaBerge GS, Bennett DC, Fain PR, Spritz RA. PTPN22 is genetically associated with risk of generalized vitiligo, but CTLA4 is not. *J Invest Dermatol* 2008;128:1757-62.
  50. Laberge GS, Birlea SA, Fain PR, Spritz RA. The PTPN22-1858C>T (R620W) functional polymorphism is associated with generalized vitiligo in the Romanian population. *Pigment Cell Melanoma Res* 2008;21:206-8.
  51. Birlea SA, Gowan K, Fain PR, Spritz RA. Genome-wide association study of generalized vitiligo in an isolated European founder population identifies SMOC2, in close proximity to IDDM8. *J Invest Dermatol* 2010;130:798-803.
  52. Boissy RE. Histology of vitiliginous skin. In: Hann S-K, Nordlund JJ, editors. *Vitiligo: monograph on the basic and clinical science*. 1<sup>st</sup> edition. Oxford, England: Blackwell Science Ltd; 2000. p. 23-34.
  53. Boissy RE. The intrinsic (genetic) theory for the cause of vitiligo. In: Hann SK, Nordlund JJ, editors. *Vitiligo: a monograph on the basic and clinical science*. Oxford: Blackwell Science Ltd; 2000. p. 123-8.
  54. Herbstman DM, Hou W, Garvan C, Wallace MR, McCormack WT. Association analysis of melanin biosynthesis genes in vitiligo susceptibility. *Exp Dermatol* 2010; In press.
  55. Alkhateeb A, Fain PR, Thody A, Bennett DC, Spritz RA. Epidemiology of vitiligo and associated autoimmune diseases in caucasian probands and their families. *Pigment Cell Res* 2003;16:208-14.
  56. Boissy RE, Manga P. On the etiology of contact/occupational vitiligo. *Pigment Cell Res* 2004;17:208-14.
  57. Boissy RE. Occupational vitiligo. In: Picardo M, Taieb A, editors. *Vitiligo*. Berlin Heidelberg: Springer-Verlag; 2010. p. 175-80.
  58. Abdel-Malek Z, Suzuki I, Tada A, Im S, Akcali C. The melanocortin-1 receptor and human pigmentation. *Ann N Y Acad Sci* 1999;885:117-33.
  59. Jee SH, Lee SY, Chiu HC, Chang CC, Chen TJ. Effects of estrogen and estrogen receptor in normal human melanocytes. *Biochem Biophys Res Commun* 1994;199:1407-12.
  60. Hall PF. The influence of hormones on melanogenesis. *Aust J Dermatol* 1969;10:125-39.
  61. Halaban R, Langdon R, Birchall N, Cuono C, Baird A, Scott G *et al*. Basic fibroblast growth factor from human keratinocytes is a natural mitogen for melanocytes. *J Cell Biol* 1988;107:1611-9.
  62. Peacocke M, Yaar M, Mansur CP, Chao MV, Gilchrist BA. Induction of nerve growth factor receptors on cultured human melanocytes. *Proc Natl Acad Sci U S A* 1988;85:5282-6.
  63. Yaar M, Eller MS, DiBenedetto P, Reenstra WR, Zhai S, McQuaid T *et al*. The trk family of receptors mediates nerve growth factor and neurotrophin-3 effects in melanocytes. *J Clin Invest* 1994;94:1550-62.
  64. Imokawa G, Miyagishi M, Yada Y. Endothelin-1 as a new melanogen: Coordinated expression of its gene and the tyrosinase gene in UVB-exposed human epidermis. *J Invest Dermatol* 1995;105:32-7.
  65. Slominski A, Tobin DJ, Shibahara S, Wortsman J. Melanin pigmentation in mammalian skin and its hormonal regulation. *Physiol Rev* 2004;84:1155-228.
  66. Quatresooz P, Hermans JF, Paquet P, Pierard GE. Mechanobiology and force transduction in scars developed in darker skin types. *Skin Res Technol* 2006;12:279-82.
  67. Picardo M, Dell'Anna ML. Oxidative stress. In: Picardo M, Taieb A, editors. *Vitiligo*. Berlin: Heidelberg: Springer-Verlag; 2010. p. 231-8.
  68. Schallreuter KU, Wood JM. Thioredoxin reductase - its role in epidermal redox status. *J Photochem Photobiol B* 2001;64:179-84.
  69. Hasse S, Gibbons NC, Rokos H, Marles LK, Schallreuter KU. Perturbed 6-tetrahydrobiopterin recycling via decreased dihydropteridine reductase in vitiligo: more evidence for H2O2 stress. *J Invest Dermatol* 2004;122:307-13.
  70. Marnett LJ. Lipid peroxidation-DNA damage by malondialdehyde. *Mutat Res* 1999;424:83-95.
  71. Takahashi A, Masuda A, Sun M, Centonze VE, Herman B. Oxidative stress-induced apoptosis is associated with alterations in mitochondrial caspase activity and Bcl-2-dependent alterations in mitochondrial pH (pHm). *Brain Res Bull* 2004;62:497-504.
  72. Dell'Anna ML, Ottaviani M, Albanesi V, Vidolin AP, Leone G, Ferraro C *et al*. Membrane lipid alterations as a possible basis for melanocyte degeneration in vitiligo. *J Invest Dermatol* 2007;127:1226-33.
  73. Schallreuter KU, Wood JM, Berger J. Low catalase levels in the epidermis of patients with vitiligo. *J Invest Dermatol* 1991;97:1081-5.
  74. Casp CB, She JX, McCormack WT. Genetic association of the catalase gene (CAT) with vitiligo susceptibility. *Pigment Cell Res* 2002;15:62-6.
  75. Liu L, Li C, Gao J, Li K, Zhang R, Wang G *et al*. Promoter variant in the catalase gene is associated with vitiligo in Chinese people. *J Invest Dermatol* 2010;130:2647-53.
  76. Dell'Anna ML, Ottaviani M, Bellei B, Albanesi V, Cossarizza A, Rossi L *et al*. Membrane lipid defects are responsible for the generation of reactive oxygen species in peripheral blood mononuclear cells from vitiligo patients. *J Cell Physiol* 2010;223:187-93.
  77. Moretti S, Fabbri P, Baroni G, Berti S, Bani D, Berti E *et al*. Keratinocyte dysfunction in vitiligo epidermis: cytokine microenvironment and correlation to keratinocyte apoptosis. *Histol Histopathol* 2009;24:849-57.
  78. Gauthier Y, Cario Andre M, Taieb A. A critical appraisal of vitiligo etiologic theories. Is melanocyte loss a melanocytorrhagy? *Pigment Cell Res* 2003;16:322-32.
  79. Mahoney JA, Rosen A. Apoptosis and autoimmunity. *Curr Opin Immunol* 2005;17:583-8.

