MELANOCYTES/MELANOGENESIS

The Genetics of Vitiligo

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doi:10.1038/skinbio.2011.7

Vitiligo is one of the most striking of all human disease phenotypes, and is perhaps the most common pigmentary disorder. The patchy loss of skin pigmentation and the marked contrast between involved and uninvolved skin particularly impacts persons of color, with consequent stigmatization that has long been recognized to result in significant social inequality and morbidity in affected individuals (Brito, 1885). Because of its visually evident cutaneous manifestations, vitiligo has been known for thousands of years. However, only relatively recently has there been real progress in understanding its pathobiological basis, which, it is hoped, may facilitate progress in vitiligo treatment and ultimately even prevention. Surprisingly, in several instances key discoveries seem to have been overlooked or discounted, only to be rediscovered and republished by others a decade or more later.

Clinical studies of vitiligo remained relatively primitive until the late 1950s, when Lerner (1959) reported the first systematic investigation of a large patient series, suggesting the descriptive classification that is still essentially in use today. In the treatment arena, repigmentation of vitiligo by topical or oral use of *Ammi majus* or *Psoralia corylifolia* plant extracts or seeds, particularly when combined with sun exposure, was known in ancient Egypt, India, China, and Japan, but was not part of Western medical practice (Lindsay, 1932). It was not until after the Second World War that specific treatment of vitiligo was pioneered by Menon (1945) in India using UV light and by El Mofty (1948) in Egypt using the crystallized active components of *Ammi majus*, mainly 8-methoxypsoralen, both alone and in combination with exposure to sunlight or UV light.

Despite extensive (and sometimes fairly wild) speculation, the pathobiology of vitiligo remained completely unknown until the next milestone, the elegant demonstration by Hu *et al.* (1959) that the affected skin of patients with generalized vitiligo, the most common form of the disorder, largely lacked melanocytes, whereas melanocytes were present in both uninvolved and repigmented skin of the same patients. These same authors also noted the transfer of pigment from melanocytes to epithelial cells following UV irradiation, which was probably the first recognition and description of what later came to be called the ''epidermal-melanin unit''. These observations led them to conclude that successful treatment of vitiligo therefore must depend on either proliferation of residual functional melanocytes within vitiligo lesions or inward migration and proliferation of melanocytes from surrounding normal skin, as well as an intact ability of epithelial cells to receive pigment from active melanocytes.

Although the specific pathogenic mechanism underlying melanocyte disappearance or destruction in vitiligo remained obscure, the earliest clue to an autoimmune origin, and perhaps the earliest milestone in vitiligo, was the report by Addison (1855) of a patient with idiopathic adrenal insufficiency, generalized vitiligo, and pernicious anemia. The frequent concomitant occurrence of multiple autoimmune diseases, including generalized vitiligo, was subsequently documented in many reports, particularly in that of Schmidt (1926), and was later codified by Neufeld and Blizzard (1980). In an 1872 lecture to the Silesian Society for National Culture, Köbner, an eccentric German dermatologist and mycologist, described the ''isomorphe Reizeffekt'' (Köbner, 1876), now known as the ''Koebner phenomenon'', the appearance of new, localized lesions at sites of skin injury in psoriasis, which was quickly extended to vitiligo and many other skin disorders that have a major autoimmune or autoinflammatory component (Hebra and Kaposi, 1874). Langhof *et al.* (1965) reported autoantibodies to melanocyte components, and Gross *et al.* (1987) identified perilesional infiltrates of cytotoxic T-lymphocytes in patients with vitiligo. There were also numerous case reports of vitiligo developing in patients with malignant melanoma, particularly in those treated by immunotherapy (Burdick and Hawk, 1964). Despite all of these indicators, there was surprisingly enduring resistance to the acceptance of generalized vitiligo as an autoimmune disease.

The role of genetic factors in vitiligo was also considered early because of the frequent clustering of cases among close relatives (Stuttgen, 1950; Teindel, 1950), and eventual genetic epidemiological studies by Das *et al.* (1985) supported multifactorial, polygenic inheritance, which currently is termed ''complex disease''. Typical of the 1960s and 1970s, ABO, haptoglobin, erythrocyte enzymes, and various serum proteins were tested as genetic markers for vitiligo, with negative results. Beginning in the 1970s, a plethora of analyses of HLA in vitiligo

were reported, with equivocal and conflicting findings. Subsequently, genetic association of vitiligo with many other candidate genes was studied and reported, though only *PTPN22* and perhaps *CTLA4*, both of which encode immune regulators, are given high credence today. The modern era of genetic studies of generalized vitiligo began indirectly, with the identification of *SLEV1* on chromosome 17p13, a linkage signal in systemic lupus erythematosus families that also included at least one relative with vitiligo (Nath *et al.*, 2001), underscoring a causal genetic relationship between these two diseases. *SLEV1* was later identified as *NLRP1* (*NALP1*), a key regulator of the innate immune system (Jin *et al.*, 2007).

The most important recent vitiligo developments were two large-scale genomewide association studies of generalized vitiligo, one in Caucasians (Jin *et al.*, 2010) and the other in Chinese (Quan *et al.*, 2010), which together identified and confirmed at least 16 different loci that contribute to generalized vitiligo susceptibility. All but one of these genes encode proteins involved in regulation of the immune system and/or have been genetically associated with susceptibility to other autoimmune diseases. The sole exception is *TYR*, encoding tyrosinase, the key enzyme of melanin biosynthesis and the principal vitiligo autoimmune antigen. In Caucasians, a common *TYR* missense variant, R402Q, confers both relative protection from generalized vitiligo and relative susceptibility to malignant melanoma, by modulating the presentation of the *TYR* peptide by HLA-A2*01, thereby modulating recognition of melanocytes by the immune system. These genes together account for a relatively small fraction of the genetic risk of generalized vitiligo, indicating that many additional vitiligo susceptibility genes undoubtedly remain to be discovered.

The results of the genetic studies thus far show that generalized vitiligo is a typical polygenic, multifactorial disorder, involving numerous different susceptibility genes, and that the great majority of these genes encode proteins that regulate or mediate recognition or destruction of melanocytes by the immune system. Coupled with the previous epidemiological and immunological evidence, there is no longer any doubt that generalized vitiligo is a complex autoimmune disease, some genes determining general susceptibility to autoimmunity, and others determining specific autoimmunity to melanocytes. These findings begin to highlight biological pathways that may mediate the response of genetically susceptible individuals to as-yet unknown environmental triggers of disease onset and their response to factors that mediate or modify its clinical course, as well as their response to treatment.

Furthermore, recent evidence suggests that immune phenomena may also contribute to the pathogenesis of ''segmental vitiligo'', a less common form of the disorder, in which melanocyte loss remains quite localized, often on the face, mostly occurring in children and usually not associated with other autoimmune diseases. Van Geel *et al.* (2010) described a lymphocytic infiltrate of interferon-γ-producing CD8+ and some CD4+ T cells at the lesional margin in early segmental vitiligo, similar to those observed in generalized vitiligo. Although occasionally segmental vitiligo and generalized vitiligo occur in the same families, it is uncertain whether this represents more than mere coincidence; thus, the true pathobiological relationship between generalized vitiligo and segmental vitiligo remains to be elucidated.

This deeper understanding of vitiligo pathogenesis allows us to anticipate future milestones. Of course, it is hoped that new insights into disease pathogenesis and pathways will provide clues to new drugs or other therapeutic approaches. However, even in the absence of new treatment modalities, such deeper understanding also dictates a reconsideration of the current approaches to vitiligo treatment. Vitiligo is a chronic autoimmune disease. Melanocyte destruction remains ongoing even during attempts at treatment, possibly accounting, in part, for the uneven therapeutic response and long-term clinical course. It may therefore prove optimal to investigate combined approaches to treatment, including both immunosuppressive and immunoregulatory approaches that aim to reduce melanocyte destruction, while also including regenerative approaches that aim to promote melanocyte repopulation of depigmented regions. Likewise, an improved understanding of what vitiligo is also helps clarify what it is not. The first Prime Minister of India, Jawaharlal Nehru, reportedly ranked vitiligo, leprosy, and tuberculosis as the three most important medical problems in India (later citations state malaria rather than tuberculosis). Particularly in India, vitiligo and leprosy have long been confused, with a consequent inappropriate stigmatization of vitiligo. In an effort to combat this erroneous stigmatization, on 27 December 2010, the Indian State of Tamil Nadu issued a Government Order that the terms ''ven kushtam'' and ''ven kuttam'', both meaning ''white leprosy'' and often used as equivalent to ''vitiligo'', should be abandoned. Truly, a milestone for Indian vitiligo patients.

CONFLICT OF INTEREST

The author states no conflict of interest.

TO CITE THIS ARTICLE

Spritz RA (2011) The genetics of vitiligo. *J Invest Dermatol* 131: E18–E20

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