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Frontiers and controversies in the pathobiology of vitiligo: separating the wheat from the chaff

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Abstract

The pathogenesis of vitiligo is complex and not well understood. Genes play a role in all aspects of vitiligo pathogenesis, and studies are ongoing to identify these genes and understand their biology. There is a body of interlocking, compelling evidence supporting an autoimmune basis for most or all cases of generalized vitiligo. The development of an autoimmune disease generally involves three components; the immune system, environmental triggers and other exogenous precipitating factors, and the target tissue. In vitiligo, precipitating factors could induce melanocyte damage in genetically susceptible individuals and consequent cell death, loss of tolerance, and induction of melanocyte-directed autoimmunity. Future research will more precisely define the multiple biological events that regulate development of vitiligo.

Keywords

autoimmunity; leukoderma; melanocytes; pigmentation

The question posed in the controversies section of *Experimental Dermatology* several issues ago (1) was ‘Vitiligo pathogenesis: autoimmune disease, genetic defect, excessive reactive oxygen species, calcium imbalance, or what else?’ The possible answers to this query are reminiscent of the infamous medical school examination multiple-choice questions: ‘some of the above’, ‘all of the above’, ‘none of the above’. In truth, we do not yet know the right answer. We can say with confidence at least ‘some of the above’, but we are not quite sure which ones, or whether there are other choices that should be on the list.

The pathogenesis of generalized vitiligo is complex and not well understood (2). Vitiligo is an acquired disorder, and it is a fundamental truism that melanocytes are lost from the involved areas, and the rate of loss must exceed the rate of replacement. However, the underlying biological phenomena are like a partially-completed jigsaw puzzle; some sections fit together and, though incomplete, show us the general outlines of part of the picture. Other bits are more fragmentary, totally missing or put together incorrectly, and it is not yet clear how everything fits together to form the total scene.

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Genes certainly play a role in all aspects of vitiligo pathogenesis, even response to environmental triggers, and so 'genetics' really should not be separated out as a distinct phenomenon. Typical generalized vitiligo behaves as a 'complex trait', the modern lingo for a polygenic, multifactorial disease involving multiple genes and non-genetic factors. By definition, 'polygenic' means that no single gene is sufficient to account for disease. We do not know how many major genes may be involved in generalized vitiligo, and in what different combinations, and only a few vitiligo susceptibility genes have been identified with reasonable certainty. Currently, there is strong support only for HLA, *PTPN22*, *NALP1* and perhaps *CTLA4*, all genes associated with autoimmune susceptibility (3), consistent with extensive evidence that generalized vitiligo is a primary autoimmune disease. Many other biological candidate genes have been suggested and studied for generalized vitiligo, but it has been an unfortunate lesson that educated genetic guesses are usually wrong, *post hoc* meta-analyses indicating that reported candidate gene 'associations' often represent population stratification and publication bias (4). Accordingly, genetic studies of complex traits have recently trended towards hypothesis-free approaches, and it is hoped that a current international genome-wide association study of generalized vitiligo will identify genes that truly are involved in disease pathogenesis and thus provide real clues to the underlying pathobiology. This is not to say that some of the genes suggested already might not be correct, but at the moment, we really do not know which might be right versus which are wrong.

In addition to the above-mentioned genetic studies showing involvement of 'autoimmunity genes' (3), there is a strong body of interlocking, compelling biological evidence supporting an autoimmune basis for most or all cases of generalized vitiligo (5,6). Generalized vitiligo is epidemiologically associated with a number of other autoimmune diseases (7,8), both in patients and in their close relatives, even those who do not themselves have vitiligo, indicative of a heritable autoimmune diathesis. Many patients with generalized vitiligo have serum autoantibodies and circulating autoreactive T cells directed against melanocytes and melanocyte components, and careful analyses of the margins of active generalized vitiligo lesions have repeatedly shown sparse infiltrates of cytotoxic T cells (5,6). Melanocytes challenged with 4-TBP express and secrete heat shock protein-70, in turn inducing TRAIL expression and activation of dendritic cells, perhaps eliciting dendritic cell effector immunological function against stressed vitiligo melanocytes (9). Numerous cases have been reported of passive transfer of generalized vitiligo following bone marrow transplantation from donors with vitiligo (10,11), and one of these authors (R.A.S.) has seen a case in which generalized vitiligo regressed dramatically during cancer chemotherapy, only to return following bone marrow recovery (unpublished data). Together, these findings illustrate the key importance of bone marrow-derived cells in disease pathogenesis, and strongly support an autoimmune basis of generalized vitiligo. While vitiligo-like depigmentation may similarly occur in the course of immunotherapy-based treatment of cutaneous melanoma, and is considered a propitious prognostic sign (2), in fact it is not clear that this phenomenon is the same as true generalized vitiligo.

Autoimmune disease is a dance involving at least three partners: the immune system, environmental triggers and other exogenous factors, and the target tissue, in this case the melanocyte. What exogenous factors damage the melanocyte or trigger the immune system to attack melanocytes in generalized vitiligo? The short answer is that we do not know. Science has developed powerful, systematic approaches to identify disease susceptibility genes, but we have no such systematic approaches to identify non-genetic, environmental triggers or precipitating factors that otherwise influence the occurrence of disease in genetically susceptible individuals. The paradigm remains one essentially of trial and error. Nevertheless, anecdotal reports of precipitating events by vitiligo patients may provide some clues that point to heritable biological properties that might make the melanocyte of some people susceptible to environmental triggers or other stressors, possibly resulting in melanocyte death by necrosis,

apoptosis or pyroptosis, consequent presentation of tolerogens and loss of immune tolerance, and ultimately autoimmunity directed against melanocytes (2,12).

Generalized vitiligo often initially involves the fingertips, knuckles, periorbital regions and perioral regions – regions of the skin that may be particularly subject to chronic mechanical abrasion. This clinical observation led to the ‘melanocytorrhagy’ hypothesis of generalized vitiligo (13), essentially that melanocytes of genetically susceptible individuals might be relatively loosely anchored to the normal dermal substratum, subject to dislodgement and consequent cell death, loss of tolerance and induction of melanocyte-directed autoimmunity. Similarly, it is striking that patients often report initial onset of generalized vitiligo at the site of skin trauma, frequently a bad sunburn or, occasionally, at the site of immunizations. This has led some to suggest that melanocytes might be overly fragile in genetically susceptible individuals (14), tissue trauma again inducing local melanocyte death, inflammation, loss of tolerance and autoimmunity. Similarly, a condition known as ‘occupational vitiligo’ sometimes occurs in individuals who encounter large doses of phenolic compounds, often in cleaning solutions (15), and it has been suggested that some individuals might be genetically susceptible to melanocyte injury from aliphatic derivatives of phenols or other common compounds encountered in the environment, resulting in generation of free radicals, cytotoxicity and melanocyte death (16), and again, loss of tolerance and autoimmunity. The sunburn connection has led others to speculate that UV might induce melanocyte-specific genes (17) such as tyrosinase, inducing melanogenesis and direct cytotoxicity due to toxic melanin intermediates (the ‘auto-cytotoxic’ hypothesis) (18) or affecting the REDOX/free radical state of the melanocyte, resulting in oxidative stress and cell damage from reactive oxygen species (19), again presumably leading to a cycle of melanocyte death and perhaps induction of autoimmunity in genetically susceptible individuals. Several other suggested theories of vitiligo pathogenesis have received little evidentiary support, and largely have fallen by the wayside. Of course, several of these or other mechanisms might be operative, perhaps in different combinations in different patients with different combinations of vitiligo susceptibility genes.

The current lack of clarity regarding vitiligo pathogenesis and the variable clinical response to current treatments creates a difficult situation for vitiligo patients and their physicians. In any disease for which the cause is unknown and effective treatment elusive, patients and physicians alike search for life events or environmental factors that might induce the disease or ameliorate its effects, providing fertile breeding ground for scientific speculation poorly grounded in evidence, and for quacks and charlatans eager to prey on desperate patients. Puberty, pregnancy, major infections, dietary or mineral imbalance, vitamin deficiency and undifferentiated ‘stress’ are the usual suspects, but despite rampant pseudoscience promulgated by the Internet, there is no compelling evidence supporting any of these as specific factors that either cause or can be used to treat generalized vitiligo. It should be remembered that until 1984 we ‘knew’ that peptic ulcers were caused by ‘stress’ and spicy foods, whereas now we know that peptic ulcers result from bacterial infection (20). The history of science is an unforgiving judge, and it is our responsibility as scientists and physicians to hold new hypotheses and treatments of vitiligo to rigorous scientific standards; otherwise, we risk being led down false paths.

And so, what is the answer to the original question, ‘Vitiligo pathogenesis: autoimmune disease, genetic defect, excessive reactive oxygen species, calcium imbalance, and what else?’ For the present, ‘Autoimmune disease, genetic defect, and maybe some of the above and other things besides’ is probably the best answer we can offer.

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