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## Vitiligo pathogenesis: autoimmune disease, genetic defect, excessive reactive oxygen species, calcium imbalance, or what else?

K. U. Schallreuter, P. Bahadoran, M. Picardo, A. Slominski, Y. E. Elassiuty, E. H. Kemp, C. Giachino, J. B. Liu, R. M. Luiten, T. Lambe, I. C. Le Poole, I. Dammak, H. Onay, M. A. Zmijewski, M. L. Dell'Anna, M. P. Zeegers, R. J. Cornall, R. Paus, J. P. Ortonne and W. Westerhof

**Abstract:** The pathobiology of vitiligo has been hotly disputed for as long as one remembers, and has been a magnet for endless speculation. Evidently, the different schools of thought – ranging, e.g. from the concept that vitiligo essentially is a free-radical disorder to that of vitiligo being a primary autoimmune disease – imply very different consequences for the best therapeutic strategies that one should adopt. As a more effective therapy for this common, often disfiguring pigmentary disorder is direly needed, we must strive harder to settle the pathogenesis debate definitively – on the basis of sound experimental evidence, rather than by a war of dogmatic theories. Recognizing, however, that it is theories which tend to guide our experimental designs and choice of study parameters, the various pathogenesis theories on

the market deserve to be critically, yet unemotionally re-evaluated. This *Controversies* feature invites you to do so, and to ask yourself: Is there something important or worthwhile exploring in other pathogenesis scenarios than those already favoured by you that may help you improve your own study design, next time you have a fresh look at vitiligo? Vitiligo provides a superb model for the study of many fundamental problems in skin biology and pathology. Therefore, even if it later turns out that, as far as your own vitiligo pathogenesis concept is concerned, you have barked-up the wrong tree most of the time, chances are that you shall anyway have generated priceless new insights into skin function along the way.

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### Prelude

#### In search of the whole truth

Four blind people encounter an elephant. One grabs the leg and is convinced it's a tree trunk. One holds the tail and thinks it's a whip. Another touches the elephant's trunk and decides it's a hose while the fourth man pats the side and is sure it's a wall.

The wise man tells them, "All of you are right." But what is the moral of this story?

Over the years, multiple aspects of biochemical, immunological, genetic and other biological aspects that play a role in the pathogenesis of vitiligo have been studied. So far, no convincing model describing the interplay of all these contributing factors has been formulated. The situation described in the old parable about four blind men and an elephant is typical for the debate on the pathogenesis of vitiligo.

For at least three decades, there have been separate, often rigidly entrenched camps of investigators defending their favourite theory – such as the auto-immune theory (1,2), the cytotoxic metabolites theory (3), the neural theory (4,5) and the genetic theory (6,7). More recently, some other theories have been added, e.g. the hydrogen peroxide theory (8,9), the growth factor theory (10,11) and the chronic pressure theory (12).

Often enough, we have witnessed the strange and unproductive situation that the researchers of one camp tried to explain vitiligo only with their own research, dealing with the key tenants of their favourite theory, while completely ignoring all the well-recognized facts supporting alternative theories.

Our group has tried to incorporate all the different causal factors that could contribute to some extent to melanocyte destruction into a 'convergence theory' (13). However,

the hierarchy of causal factors and their interdependence in the pathogenesis process were at that time absolutely unclear to us.

The problem with all existing theories is that, despite extensive basic research, no conclusive proof exists to demonstrate how exactly epidermal melanocytes are actually killed by the proposed cytotoxic agent or mechanism.

**1** The auto-immune theory was lacking the knowledge about the precise antigenic structure. There were indications of a cell-mediated immune process, a certain required predisposition for a genetic make-up, e.g. HLA-A2 expression, and the involvement of some differentiation antigen of melanocytes, e.g. tyrosinase, TRP1 or TRP2. However, it is an iron-clad rule that self-antigens, normally, do not produce harmful immune reactions. Otherwise, we would not be here. Researchers have tried to alter the antigenic structure of these self-antigens, including MART1/Melan-A, Pmel17/gp100 or gp75 or preferably small peptide chains derived from it. Research aimed at developing anti-melanoma vaccines, have so far been unsuccessful to develop an effective immune response in patients. Apparently, nature's idea of foreign is not easy to copy.

**2** The biochemical theory due to either (exogenous) monobenzene-like substances or (endogenous) catechols like noradrenaline or semi-quinones of estrogens has never been tested in an appropriate animal model to provide a convincing proof of principle, i.e. to demonstrate that the reported intracellular concentrations of these molecules actually lead to melanocyte cell death *in vivo*. Research indicates that the cytotoxicity of these reactive *o*-quinones is similar for melanocytes, keratinocytes as well as renal and hepatic cells. Furthermore, it has never been shown that the metabolism of these endogenous catechols and semi-quinones only occurs in melanocytes, leaving the apparently exclusive cytotoxicity happening in melanocytes unexplained.

**3** The oxidative stress theory, circling around raised levels of hydrogen peroxide, suffers from similar problems. Here, the molecule is so tiny and highly diffusible, similar to oxygen, that it is difficult to see how a sharply defined pathogenic gradient could possibly be generated. Therefore, also in this example, one would expect deleterious effects towards the entire skin, if not the whole system, which should even have lethal consequences.

The genetic theory is, of course, based on defect(s) in the expression of genes controlling the above-described mechanisms.

On the basis of the currently existing research, and incorporating all known key facts of the above-mentioned

'separatist' theories, we now propose a refined 'convergence theory', according to which vitiligo has a multi-factorial aetiology, characterized by multiple sequential pathogenesis steps.

The first step is always an increase in endogenous (e.g. metabolites of noradrenalin, semiquinone of estrogens, etc.) or exogenous phenol/catechol concentration (e.g. monobenzene or related molecules) in the melanocyte environment, serving as a preferred surrogate substrate of tyrosinase, competing with its physiological substrate, tyrosine. The conversion of these substrates into reactive quinones is reinforced by a disturbed redox balance (increasing hydrogen peroxide). Such reactive quinones then covalently bind to the catalytic centre of tyrosinase (haptentation).

This could give rise to a new antigen, carried by Langerhans cells to the regional lymph node, stimulating the proliferation of cytotoxic T cells through an apoptotic process – provided that the immunogenetic make-up of the individual fits (e.g. in HLA-A2-positive individuals).

However, the activation of melanocyte-targeting cytotoxic T cells is only a first step in skin melanocyte killing. Spreading of the disease depends on a shift in the balance between immune defence and tolerance, e.g. resulting from a decrease in properly functioning T-regulatory cells (14).

In conclusion, we now consider vitiligo to represent a complex reaction pattern or a syndrome, involving multiple etiologic factors, some of them necessarily working in concert.

**Wiete Westerhof**

Netherlands Institute for Pigment Disorders, Amsterdam,  
The Netherlands; E-mail: w.westerhof@amc.uva.nl

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