

Analysis of the Cause of Chemical Induced Contact/Occupational Vitiligo

Raymond E. Boissy, PhD
Prashiela Manga, PhD
Professor & Assistant Professor of Dermatology
University of Cincinnati College of Medicine, Cincinnati OH

During the past several months we have been continuing our analysis of the cause of chemical induced contact/occupational vitiligo. Melanocytes of the skin can be preferentially destroyed by phenol derivatives such as 4-(tert)butylphenol (4-TBP). Exposure to 4TBP, an antioxidant/plasticizer frequently added to some industrial oils, rubber, adhesives and germicidal detergents, can result in chemical Leukoderma in some individuals and Vitiligo in a smaller subset.

We have previously demonstrated that 4TBP is preferentially cytotoxic to melanocytes maintained in culture and have now confirmed that exposure of these cultured melanocytes to 4TBP results in a dose-dependent initiation of a specialized form of cell death termed apoptosis. Because the chemical structure of 4TBP resembles the molecule used by the melanocyte to make melanin (i.e., tyrosine), it was previously thought that the major enzyme in this process (i.e., tyrosinase) was responsible for converting 4TBP into a toxic by product that caused melanocyte apoptosis. However, we had shown about a year ago that tyrosinase expression and activity had not affected the damage that 4TBP could do to the melanocyte.

Therefore, our current research studies have focused on another enzyme specifically made by the melanocytes that is also important in the formation of pigment. This molecule is called Tyrosinase Related Protein-1 (Typr1) and its specific role in human melanin synthesis is unknown. However, melanocytes that do not make Typr1 cannot synthesize much pigment and people inheriting this Typr1 deficiency express a form of albinism called Oculocutaneous Albinism Type3 (i.e., OCA3). We have recently obtained experimental data that suggests Typr1 may indeed interact with 4TBP to cause the death of melanocytes.

Our specific data is as follows.

We initially compared the effect of 4TBP on melanocytes cultured from normally pigmented individuals with melanocytes from individuals with OCA3. OCA3 melanocytes were found to be more resistant to 4TBP induced apoptosis. In contrast, fibroblasts cultured from individuals with OCA3 were equally sensitive to 4TBP as control fibroblasts. We subsequently manipulated experimentally the amount of Typr1 in melanocytes and correlated their response to 4TBP exposure. A line of cultured melanoma cells were transfected with DNA encoding a normal or a mutant, defective form of Typr1 so that the resulting melanoma cells expressed more normal versus nonfunctional Typr-1 respectively. The result was that the melanoma cells expressing more Typr-1 were more easily killed by 4TBP than either the normal melanoma cells or the melanoma cells expressing much nonfunctional Typr-1.

These studies clearly confirm that Typr1 mediates melanocyte cell death that can be caused by exposure to phenolic derivatives like 4TBP in normal human melanocytes. We now will begin to explore how this melanocyte specific protein, Typr1, functions in this capacity. However, of more importance is the question of whether this process is involved in the premature melanocyte death that appears to be the basis for contact/occupational Vitiligo in specific and generalized vitiligo. We plan to evaluate the sensitivity of 4TBP towards Vitiligo melanocytes and the associated function of Typr1 in this situation. We predict that the amount and/or regulation of Typr1 by Vitiligo melanocytes is altered, thus causing Vitiligo melanocytes to be more easily destroyed by cytotoxic agents like 4TBP.

A number of events have been shown to precipitate vitiligo, leading investigators to propose that melanocytes in the skin of Vitiligo patients are inherently more fragile than melanocytes from healthy skin. One potential mechanism responsible for this fragility may be a reduced ability to combat oxidative stress. Previous studies have shown increased levels of the oxidant hydrogen peroxide and reduced levels of the potent antioxidant catalase in the skin from vitiligo patients. We will investigate the possibility that environmental insults, such as exposure to 4-tert butyl phenol, does not elicit appropriate activation of antioxidant pathways in Vitiligo melanocytes, preventing cells from mounting a defense against oxidants, thereby triggering programmed cell death.