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References

- 1 Taieb A. *Pigment Cell Res* 2000; **13** (Suppl 8): 41–47.
- 2 Huang C L *et al.* *Am J Clin Dermatol* 2002; **3**: 301–308.
- 3 Nordlund J J, Majumder P P. *Dermatol Clin* 1997; **15**: 69–78.
- 4 Le Poole I C *et al.* *J Invest Dermatol Symp Proc* 2004; **9**: 68–72.
- 5 Schallreuter K U *et al.* *J Invest Dermatol Symp Proc* 1999; **4**: 91–96.
- 6 Dell'Anna M L, Picardo M. *Pigment Cell Res* 2006; **19**: 406–411.
- 7 Boissy R E, Manga P. *Pigment Cell Res* 2004; **17**: 208–214.
- 8 Slominski A *et al.* *J Royal Soc Med* 1989; **82**: 539–541.
- 9 Slominski A *et al.* *Physiol Rev* 2004; **84**: 1155–1228.
- 10 Schallreuter K U *et al.* *Biochem Biophys Res Commun* 2007; **360**: 70–75.
- 11 Carlberg C. *Ann N Y Acad Sci* 2000; **917**: 387–396.
- 12 Dubocovich M L *et al.* *Front Biosci* 2003; **8**: d1093–d1108.
- 13 Slominski A *et al.* *J Cell Physiol* 2003; **196**: 144–153.
- 14 Slominski A *et al.* *Endocrine* 2005; **27**: 137–148.
- 15 Kobayashi H *et al.* *FASEB J* 2005; **19**: 1710–1712.
- 16 Slominski A *et al.* *FASEB J* 2002; **16**: 896–898.
- 17 Slominski A *et al.* *FASEB J* 2005; **19**: 176–194.
- 18 Fischer T W *et al.* *FASEB J* 2006; **20**: 1564–1566.
- 19 Reiter R J *et al.* *Acta Biochim Pol* 2007; **54**: 1–9.
- 20 Tan D X *et al.* *J Pineal Res* 2007; **42**: 28–42.
- 21 Pandi-Perumal S R *et al.* *FEBS J* 2006; **273**: 2813–2838.
- 22 Semak I *et al.* *Biochemistry* 2005; **44**: 9300–9307.
- 23 Leon J *et al.* *J Pineal Res* 2005; **38**: 1–9.
- 24 Nosjean O *et al.* *J Biol Chem* 2000; **275**: 31311–31317.
- 25 Fischer T W *et al.* *J Pineal Res* 2006; **40**: 18–26.
- 26 Fischer T W, Elsner P. *Curr Probl Dermatol* 2001; **29**: 165–174.
- 27 Fischer T W *et al.* *Skin Pharmacol Appl Skin Physiol* 2002; **15**: 367–373.
- 28 Ryou Y W *et al.* *J Dermatol Sci* 2001; **27**: 162–169.

Commentary 1

The aetiology and pathogenesis of the skin-depigmenting disease vitiligo has long been the subject of both research and debate. Currently, the exact cause of vitiligo remains obscure, but many factors have been implicated in its development including infections, stress, neural abnormalities, melatonin receptor dysfunction, impaired melanocyte migration, genetic susceptibility, biochemical defects and autoimmunity (1,2). Ultimately, these different factors could act independently or together to yield the same effect, namely the disappearance of melanocytes from the skin and this is proposed in the convergence theory (1). For example, autoimmunity might arise as a secondary phenomenon following the self-destruction of pigment cells due to biochemical imbalances and this might then amplify the damage to melanocytes.

Autoimmunity involvement in vitiligo aetiology is supported by several lines of evidence. Predisposition to vitiligo appears to be associated with certain alleles of the major histocompatibility complex (MHC) class II antigens as well as with other autoimmune-susceptibility genes (3–5). Furthermore, the association of vitiligo with various autoimmune disorders, animal models of the disease and the positive response to immunosuppressive therapeutic agents emphasize the role of autoimmunity in the development of this disorder (6). Moreover, autoantibodies and autoreactive T cells against cutaneous melanocytes have been identified in patients with vitiligo (7,8). Circulating melanocyte-specific cytotoxic T lymphocytes expressing high levels of the skin-homing receptor cutaneous lymphocyte-associated antigen at frequencies correlating with both

the extent and activity of the disease have been detected in patients with vitiligo (8,9). In addition, perilesional T-cell clones derived from patients with vitiligo exhibit a predominant type 1-like cytokine secretion profile and also display anti-melanocyte cytotoxicity (10).

Autoantibodies that are able to destroy melanocytes *in vitro* by complement-mediated damage and antibody-dependent cell-mediated cytotoxicity and *in vivo* following passive immunization of nude mice grafted with human skin are found in patients with vitiligo (11,12). Furthermore, IgG purified from patients with vitiligo can destroy melanoma cells both *in vitro* and *in vivo* (13), and vitiligo anti-melanocyte IgG antibodies can induce HLA-DR and intercellular adhesion molecule-1 expression on and interleukin-8 release from pigment cells (14), changes that may enhance the antigen-presenting activity of the cells allowing antigen-specific immune effector cell attack resulting in the destruction of melanocytes.

Despite detailed studies that implicate autoreactive T cells and autoantibodies in vitiligo pathogenesis, the exact contribution that they play in the destruction of melanocytes during development of the disease remains to be determined. Of particular interest is whether aberrant immune responses are of primary origin or whether they constitute a secondary reaction. A genetic predisposition to immune dysregulation at the T- or B-cell level could lead to the production of autoreactive T cells or autoantibodies that destroy melanocytes. Alternatively, autoreactive T cells or autoantibodies against melanocytes could arise in response to a challenge to the immune system. For

example, antigens released from pigment cells disrupted by non-immune mechanisms could initiate immune reactivities that target melanocytes which then exacerbate the disorder. Indeed, interestingly, melanocyte-specific cytotoxic T lymphocytes and autoantibodies have been identified in patients with melanoma where vitiligo has occurred during immunotherapy with specific pigment cell antigens (15,16). Of course, melanocytes could also come under attack from immune responses if they expose antigens that are similar to either an infectious agent or to other cells that are themselves the primary target of the autoreactive T cells or autoantibodies.

Alongside the autoimmune hypothesis, the theory that metabolic deregulation can lead to the production of toxic metabolites that damage melanocytes resulting in vitiligo is well documented and supported by much evidence. The biochemical hypothesis argues that the destruction of melanocytes is due to the accumulation of toxic metabolites from melanogenesis, the break down of free-radical defense and an excess of hydrogen peroxide (17–20). Notably, new *in vitro* studies have provided a link and a temporal sequence connecting cellular oxidative stress and the immune response in vitiligo: stressed melanocytes were found to mediate dendritic cell activation with the consequent dendritic cell effector functions playing a role in the destruction of pigment cells. This work suggests that intrinsic damage to pigment cells could be the initiating event in the development of vitiligo followed by a secondary immune response which exacerbates the destruction of melanocytes and progresses the disease (21) and as such supports the proposed convergence theory (1).

Undoubtedly, the genetic influence on the development of vitiligo is strong and evidence for the contribution of biochemical defects and autoimmunity on the development

of the disease is substantial. Overall, further research regarding the aetiology of vitiligo is required to determine the exact contribution that different factors make to initiation of the disease. This should lead to an improvement in therapeutic modalities and will also aid in setting the criteria for clinical classification of the disease as different pathogenic mechanisms could account for the various clinical types of vitiligo (2).

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References

- 1 Le Poole I C *et al.* *Exp Dermatol* 1993; **2**: 145–153.
- 2 Taieb A. *Pigment Cell Res* 2000; **13** (Suppl. 8): 41–47.
- 3 Fain P R *et al.* *Pigment Cell Res* 2006; **19**: 51–57.
- 4 Alkhateeb A *et al.* *Hum Mol Genet* 2002; **11**: 661–667.
- 5 Spritz R A *et al.* *Am J Hum Genet* 2004; **74**: 188–191.
- 6 Kemp E H *et al.* *Autoimmunity* 2001; **34**: 65–77.
- 7 Naughton G K *et al.* *J Exp Med* 1983; **158**: 246–251.
- 8 Ogg G S *et al.* *J Exp Med* 1998; **188**: 1203–1208.
- 9 Lang K S *et al.* *J Invest Dermatol* 2001; **116**: 891–897.
- 10 Wankowicz-Kalinska A *et al.* *Lab Invest* 2003; **83**: 683–695.
- 11 Norris D A *et al.* *J Invest Dermatol* 1988; **90**: 783–789.
- 12 Gilhar A *et al.* *J Invest Dermatol* 1995; **105**: 683–686.
- 13 Fishman P *et al.* *Cancer* 1993; **72**: 2365–2369.
- 14 Yi Y L *et al.* *J Invest Dermatol* 2000; **115**: 969–973.
- 15 Okamoto T *et al.* *J Invest Dermatol* 1998; **111**: 1034–1039.
- 16 Yee C *et al.* *J Exp Med* 2000; **192**: 1637–1644.
- 17 Pawelek J *et al.* *Nature* 1980; **286**: 617–619.
- 18 Schallreuter K U *et al.* *J Invest Dermatol* 1991; **97**: 1081–1085.
- 19 Dell'Anna M L, Picardo M. *Pigment Cell Res* 2006; **19**: 406–411.
- 20 Schallreuter K U *et al.* *Mol Genet Metab* 2005; **86**: S27–S33.
- 21 Kroll T M *et al.* *J Invest Dermatol* 2005; **124**: 798–806.

Commentary 2

Vitiligo is an acquired depigmentation disorder affecting 0.5–2% of the world population. Multiple theories of pathogenesis exist, and some support exists for an autoimmune aetiology (1). This hypothesis proposes that an immune system disorder results in the destruction of melanocytes. It is first supported by the frequent observation that several autoimmune disorders (thyroid diseases, Addison's disease, etc.) are associated with vitiligo. A significant association of vitiligo was demonstrated with thyroid dysfunction and/or thyroid antibodies in particular (1).

Concerning humoral immunity, antibodies to surface and cytoplasmic antigens of melanocytes have been found in patients with vitiligo, mainly belonging to the IgG class. The autoantigens most frequently identified are antigens related to HLA class I molecules, tyrosinase, tyrosinase-related protein (TRP)-1 and TRP-2 (the last three are

melanocyte-specific antigens) (2). However, the pathogenic role of antimelanocyte antibodies remains unclear. The serum levels of antibodies to melanocyte antigens seem to correlate with activity and extent of the disease and with the presence of other immune disorders, and to decrease in patients with vitiligo responding to therapy (2).

A very recent and large epidemiological study supports the involvement of both genetic and non-genetic factors in the pathogenesis of the disease (3). A positive family history for vitiligo is reported. Actually, family clustering of cases is not uncommon, as about 20% of patients have at least one affected first-degree relative, with a non-Mendelian pattern suggestive of multifactorial, polygenic inheritance (4); segregation analyses suggest the involvement of multiple interacting genes in different populations (5). Several genes and chromosomal regions have been implicated