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Autoimmunity in Vitiligo

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1. Introduction

Vitiligo is an idiopathic disorder of pigmentation characterised by the presence of depigmented skin macules due to the chronic and progressive loss of melanocytes from the cutaneous epidermis. Large population surveys have shown a worldwide incidence of 1-2% (Boisseau-Garsaud et al., 2000; Howitz et al., 1977; Majumder et al. 1993; Mehta et al., 1973), although a prevalence of 8.8% has been reported in India (Sehgal & Srivastava, 2007). The disease occurs independently of age and race, and both sexes are equally affected (Behl et al., 2003; Cho et al., 2000; Handa & Dogra, 2003; Hann & Lee, 1996; LePoole & Boissy, 1997; Zaima & Koga, 2002). In approximately half of all cases, vitiligo appears before the age of 20 years, and 70-80% of patients develop the disease by the age of 30 years (Behl et al., 2003; Herane, 2003). Frequently, patients with vitiligo also suffer from other autoimmune conditions (Alkhateeb et al., 2003; Laberge et al., 2005).

Usually, vitiligo is viewed as a minor disease, but the impact on patients' psychological well-being and social interactions is often underestimated (Kent & Al' Abadie, 1996; Ongenae et al., 2006; Porter et al., 1986). The treatment of choice in vitiligo is dependent upon factors which include vitiligo type (non-segmental, segmental), patient age, and location and stability of depigmented lesions (Taieb & Picardo, 2010). However, despite the many available therapeutic modalities (Abu Tahir et al., 2010; Olsson, 2010), repigmentation in the majority of vitiligo patients is rarely complete or long-lasting, so a better understanding of the precise aetiology and pathogenesis of the disease is crucial to improving the efficacy of treatment regimens.

Currently, the exact aetiology of vitiligo remains obscure, but many factors have been implicated in the development of the disease including infections (Grimes et al., 1996; Shegan, 1971), stress (Al'Abadie et al., 1994a), neural abnormalities (Al'Abadie et al., 1994b), defective melanocyte adhesion (Gauthier et al., 2003), and genetic susceptibility (Spritz, 2010). The biochemical hypothesis argues that melanocyte destruction is due to the accumulation of toxic metabolites from melanogenesis, the break-down of free-radical defence and an excess of hydrogen peroxide (Dell'Anna & Picardo, 2006; Schallreuter et al., 1991; Schallreuter et al., 2001; Schallreuter et al., 2005). In addition, many studies have indicated a role for both cellular (Ogg et al., 1998; Van den Boorn et al., 2009; Wankowicz-Kalinska et al., 2003) and humoral (Gilhar et al., 1995; Naughton et al., 1983a; Norris et al., 1988a) immunity in the pathogenesis of vitiligo. Ultimately, these different factors may 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 (Le Poole et al., 1993a). For example, autoimmunity might arise as a secondary phenomenon following the self-destruction of pigment cells and this might then amplify the damage to melanocytes. In addition, different pathogenic mechanisms could account for the various clinical types of vitiligo: the possible neural mechanisms are usually related to segmental vitiligo, whereas autoimmunity is most often associated with the non-segmental (generalised) form (Taieb, 2000).

2. Immunological factors in vitiligo aetiology and pathogenesis

The evidence for the role of autoimmunity in the aetiology and pathogenesis of vitiligo will be discussed in the next sections.

2.1 Immuno-genetic factors

The majority of cases of vitiligo are sporadic without a family history of the disease. Nevertheless, 15-20% of patients report at least one affected first-degree relative (Alkhateeb et al., 2003), lending evidence for a genetic role in the aetiology of vitiligo. Furthermore, among Caucasians, the risk of vitiligo developing in a patient's sibling is approximately 6.1% (Alkhateeb et al., 2003), an increase of 16-fold compared to the general Caucasian population where the prevalence of the disease is 0.38% (Howitz et al., 1977). Similarly, an increased risk among first-degree relatives is found in Indian-Pakistanis at 6.1% (Alkhateeb et al., 2003), in American Hispanic-Latinos at 4.8% (Alkhateeb et al., 2003) and in Han Chinese at 2.6% (Sun et al., 2006). A simple Mendelian inheritance pattern is not displayed in these familial aggregations of vitiligo cases (Alkhateeb et al., 2003; Bhatia et al., 1992; Carnevale et al., 1980; Das et al., 1985; Hafez et al., 1983; Laberge et al., 2005; Majumder et al., 1988; Majumder et al., 1993; Mehta et al., 1973; Nath et al., 1994; Sun et al., 2006), suggesting that the disease is probably transmitted as a polygenic trait. Indeed, earlier disease onset in familial cases (Alkhateeb et al., 2003; Laberge et al., 2005) and reduced risk of vitiligo with increasing genetic distance from the patient (Alkhateeb et al. 2003) are indicative of a polygenic disorder. Formal genetic segregation analyses of vitiligo have also suggested that multiple loci contribute to vitiligo susceptibility (Majumder et al., 1993; Nath et al., 1994; Sun et al., 2006). Seldomly have large multi-generation families been reported where vitiligo segregates in an autosomal dominant pattern (Alkhateeb et al., 2005). Twin studies have also provided evidence of a genetic component to vitiligo aetiology. For vitiligo in monozygotic twins, the concordance is 23% (Alkhateeb et al. 2003), a disease risk that is 60-fold greater than that in the general population (Howitz et al., 1977) and 4-fold higher than that for a patient's sibling (Alkhateeb et al., 2003).

The genetic epidemiological evidence has prompted the search for genes which predispose an individual to vitiligo. Investigations have included families with vitiligo as well as cohorts of patients without a familial history of the disease (Cantón et al., 2005; Fain et al., 2003). In addition, different approaches have been employed to identify genes which confer susceptibility to vitiligo including candidate gene association studies (Blomhoff et al., 2005; Cantón et al., 2005), genome-wide linkage studies (Chen et al., 2005; Fain et al., 2003; Liang et al., 2007; Spritz et al., 2004), and genome-wide association studies (Birlea et al., 2010; Jin et al., 2010a; Quan et al., 2010). The majority of genes and genetic loci so far identified have a role in the function of the immune system (Spritz, 2010), and these are summarised in the following sections.

2.1.1 Human leukocyte antigen alleles of the major histocompatibility complex

Initial case-control analyses demonstrated an association between predisposition to vitiligo and several different human leukocyte antigen (HLA) alleles of the major histocompatibility complex (MHC), and these are summarised in Table 1. Although these studies showed weak and variable associations, a significant association of HLA-DR4 and vitiligo was demonstrated in several populations (Dunston et al. 1990; Foley et al. 1983; Venneker et al. 1992) and a subsequent meta-analysis of a series of case-control studies reported association of vitiligo with HLA-A2 (Liu et al., 2007).

Population	Associated HLA Allele	Reference
American (Caucasian)	DR4	Foley et al., 1983
American (African)	DR4, DQw3	Dunston et al., 1990
American and British (European-derived, Caucasian)	DRB1A*04-DQB1*0301	Fain et al., 2006
American and British (European-derived, Caucasian)	Class I (specifically A*0201) and II antigens	Jin et al., 2010a
Chinese (Han)	DQA1*0302, DQB1*0303, DQB1*0503	Yang et al., 2005
Chinese (Han)	A25-Cw*0602-DQA1*0302	Xia et al., 2006
Chinese (Han and Uygar)	Class I and II antigens	Quan et al., 2010
Dutch	DR4, DR6, Cw6	Venneker et al., 1993; Venneker et al., 1992
Dutch	DRB4*0101, DQB1*0303	Zamani et al., 2001
German (Northern)	A2	Schallreuter et al., 1993
Hungarian	DR1, DR3	Poloy et al., 1991
Italian	A30, B27, Cw6, DQw3	Finco et al., 1991
Italian (Northern)	A3	Lorini et al., 1992
Italian (Northern)	A30, Cw6, DQw3	Orecchia et al., 1992
Japanese	A31, Bw46, Cw4	Ando et al., 1993
Kuwaiti	B21, Cw6	Al-Fouzan et al., 1995
Moroccan (Jewish)	B13	Metzker et al., 1980
Omani	Bw6, DR7	Venkataram et al., 1995
Slovak	A2, Dw7	Buc et al., 1996
Turkish	DRB1*03, DRB1*04, DRB1*07	Tastan et al., 2004
Yemeni	Bw35	Metzker et al., 1980

Table 1. Association of human leukocyte antigen (HLA) alleles with vitiligo susceptibility

More recently, the use of better analytical and statistical methods has revealed associations of vitiligo with HLA-DRB1*04, HLA-DRB1*03 and HLA-DRB1*07 alleles in Turkish patients (Tastan et al., 2004), with HLA-DRB4*0101 and HLA-DQB1*0303 in Dutch patients (Zamani

et al., 2001), and HLA-A25-Cw*0602-DQA1*0302, HLA-DQA1*0302, HLA-DQB1*0303 and HLA-DQB1*0503 in Han Chinese patients (Xia et al., 2006; Yang et al., 2005). Furthermore, a study of 76 Caucasian multiplex vitiligo families found the HLA-DRB1A*04-DQB1*0301 haplotype to be associated with a higher risk of developing vitiligo and with an earlier onset of the disease (Fain et al., 2006). Finally, two genome-wide association studies undertaken on populations of vitiligo patients have reported that predisposition of vitiligo is associated with HLA class I and II antigens (Jin et al., 2010a; Quan et al., 2010).

2.1.2 Immune-response genes and loci

Variations in several immune-response genes, including CCR6, FOXP1, FOXP3, TSLP and XBP1, have a confirmed association with predisposition to vitiligo and these are summarised in Table 2 (Birlea et al., 2011; Cheong et al., 2009; Jin et al., 2010a; Jin et al., 2010b; Quan et al., 2010; Ren et al., 2009). Of particular note, the allelic variation R620W of the PTPN22 gene, which encodes lymphoid protein tyrosine phosphatase, a molecule involved in T cell signalling, has been shown to confer vitiligo susceptibility in several independent reports (Cantón et al., 2005; Jin et al., 2010a; Laberge et al., 2008a; Laberge et al., 2008b). In addition, allelic variants in the NLRP1 gene (previously NALP1 or SLEV1), which encodes a key regulator of the innate immune system, have been reproducibly associated with an increased risk of vitiligo in different populations (Jin et al., 2007a; Jin et al., 2007b; Nath et al., 2001; Spritz et al., 2004).

The study of variations in the cytotoxic T lymphocyte antigen 4 (CTLA4) gene has yielded conflicting results with respect to vitiligo susceptibility (Birlea et al., 2011; Birlea et al., 2009; Blomhoff et al., 2005; Deeba et al., 2010; Itirli et al., 2005; Kemp et al., 1999; Laberge et al., 2008a; Pehlivan et al., 2009). Presently, allelic differences in CTLA4 appear to be predominantly associated with vitiligo occurring together with other autoimmune diseases (Blomhoff et al., 2005), and it has been suggested, therefore, that the association of CTLA4 with vitiligo is probably secondary to its primary association with disorders such as autoimmune thyroid disease (Spritz, 2010).

2.2 Associated autoimmune disease

Vitiligo is frequently associated with other autoimmune disorders, particularly autoimmune thyroid disease (Boelaert et al., 2010; Ochi & DeGroot, 1969), autoimmune polyendocrine syndromes (Ahonen et al., 1990; Neufeld et al., 1990), pernicious anaemia (Dawber, 1970), Addison's disease (Zelissen et al., 1995), and alopecia areata (Ahmed et al., 2007). Furthermore, patients with vitiligo are more likely to suffer from autoimmune conditions than those in the general population (Birlea et al., 2008; Cunliffe et al., 1968; Liu et al., 2005; Turnbridge et al., 1977). In a survey of more than 2,600 unselected Caucasian vitiligo patients, elevated frequencies of autoimmune thyroid disease, Addison's disease, systemic lupus erythematosus and pernicious anaemia were found, with approximately 30% of patients being affected with at least one additional autoimmune disorder (Alkhateeb et al., 2003). Moreover, these same autoimmune diseases occurred at an increased frequency in the first-degree relatives of the patients studied (Alkhateeb et al., 2003). Similarly, in multiplex generalised vitiligo families, higher frequencies of psoriasis, rheumatoid arthritis and type 1 diabetes mellitus were noted in addition to autoimmune thyroid disease, Addison's disease, systemic lupus erythematosus and pernicious anaemia (Laberge et al., 2005). Such data indicate that individuals can be genetically predisposed to a specific group of autoimmune diseases that includes vitiligo, and are also evidence for an autoimmune aetiology for this depigmenting disorder.

Gene or Locus	Function/Comment	Reference
AIS2	Autoimmune susceptibility locus 2. Function undefined. Associated with autoimmune disease.	Spritz et al., 2004
CCR6	Cytokine-chemokine receptor for CCL20. Recruits immune cells on binding of ligand. Associated with inflammatory bowel disease.	Jin et al., 2010a; Jin et al., 2010b; Quan et al., 2010
C1QTNF6	C1q and tumour necrosis factor-related protein- 6. Associated with rheumatoid arthritis and type 1 diabetes mellitus.	Jin et al., 2010a
FOXP1	Forkhead box P1. Transcription factor which regulates development of immune cells.	Jin et al., 2010a; Jin et al., 2010b
FOXP3	Forkhead box P3. Transcription factor which regulates regulatory T cell development. Causes autoimmune IPEX syndrome.	Birlea et al., 2011
GZMB	Granzyme B. Regulates cell-mediated immune responses.	Jin et al., 2010a
IL2RA	Interleukin (IL)-2 receptor alpha chain. Receptor for cytokine IL2 which induces T and B cell proliferation. Associated with many autoimmune diseases.	Jin et al., 2010a
LPP	LIM domain-containing preferred translocation partner in lipoma. Function unknown. Associated with celiac disease and rheumatoid arthritis.	Jin et al., 2010a
NLRP1 (NALP1; SLEV1)	NACHT leucine-rich-repeat protein 1. Functions in the innate immune response. Associated with many autoimmune diseases.	Jin et al., 2007a; Jin et al., 2007b; Nath et al., 2001; Spritz et al., 2004
PTPN22	Lymphoid protein tyrosine phosphatase. Negatively regulates T cell activation. Associated with many autoimmune diseases.	Cantón et al., 2005; Jin et al., 2010a; Laberge et al., 2008a; Laberge et al., 2008b
TSLP	Thymic stromal lymphopoietin. Cytokine which induces naïve CD4+ T cells to produce T helper cell 2 cytokines.	Birlea et al., 2011; Cheong et al., 2009
UBASH3A	Ubiquitin-associated and SH3 domain-containing A gene. Regulates T cell receptor signalling. Associated with type 1 diabetes mellitus.	Jin et al., 2010a
XBP1	X-box binding protein 1. Transcription factor which regulates MHC class II gene expression. Associated with inflammatory bowel disease.	Birlea et al., 2011; Ren et al., 2009

Table 2. Confirmed associations of immune-response gene variants with vitiligo susceptibility

2.3 Animal models

The study of animal models has added credence to the theory that immune mechanisms play a part in the development of vitiligo. Several spontaneous animal models of vitiligo exist, although the exact relevance of such models to the equivalent human disorder remains to be established (Boissy & Lamoreux, 1988). The well-documented Smyth chickens express a genetically inherited form of vitiligo-like depigmentation resulting from the loss of melanocytes in feather and ocular tissues (Smyth, 1989). In this avian model, vitiligo begins with an inherent melanocyte defect that is followed by an autoimmune response involving both humoral and cellular reactions that eliminate abnormal pigment cells (Boissy et al., 1984; Boyle et al., 1987; Lamont & Smyth, 1981; Pardue et al., 1988). An increase in T cells in the feather pulp and circulating inflammatory leukocytes has been shown in Smyth chickens prior to the onset, and during the development of, vitiligo (Erf & Smyth, 1996; Erf et al., 1995). Antibodies to chicken melanocytes have also been detected in the sera of 100% of Smyth chicks but not in the sera of normally pigmented birds (Austin et al., 1992). These antibodies were found to be present both before and during the presentation of vitiligo (Searle et al., 1991), and the primary target antigen was identified as the melanogenic enzyme tyrosinase-related protein-1 (Austin & Boissy, 1995). In other animals with vitiligo including horses, cats and dogs, antibody reactivity occurs against a similar pattern of melanocyte antigens to that found in patients with the disease (Naughton et al., 1983b; Naughton et al., 1986a), suggesting that similar immunological responses occur in both animals and humans.

2.4 Vitiligo melanocytes

Several studies have shown abnormal expression of MHC class II antigen HLA-DR and increased expression of intercellular adhesion molecule-1 by perilesional melanocytes in vitiligo compared with melanocytes from normal skin (Al Badri et al., 1993a; Hedley et al., 1998; Van den Wijngaard et al., 2000). Since these molecules have important roles in antigen presentation and in the activation of helper T cells, their expression by melanocytes could contribute to the anti-melanocyte cellular immune responses that are seen in vitiligo (Ogg et al., 1998; Van den Boorne et al., 2009). Both vitiligo and normal melanocytes are also capable of expressing MHC class I molecules (Hedley et al., 1998), which could allow interaction with destructive cytotoxic T cells. Furthermore, melanocytes have an antigen processing and presenting capability which can make them target cells for T cell-mediated cytotoxicity (Le Poole et al., 1993b). In perilesional vitiligo biopsies, melanocytes express macrophage markers CD68 and CD36 (Van den Wijngaard et al., 2000) and reduced levels of membrane regulators of complement activation, including decay acceleration factor and membrane cofactor protein (Van den Wijngaard et al., 2002), which suggests a vulnerability of these cells to attack by macrophages and the complement system, respectively.

2.5 Vitiligo treatments

Repigmentation in vitiligo patients receiving treatment with immunosuppressive agents indirectly supports the theory that immune-mediated processes are involved in vitiligo pathogenesis. Topically applied tacrolimus (FK506), a therapeutic agent which exerts a potent immunosuppressive effect on T cells by blocking the action of the cytokine gene-activating cofactor calcineurin (Homey et al., 1998), has resulted in successful repigmentation responses in vitiligo patients (Boone et al., 2007; Hartmann et al., 2008).

Topical corticosteroids, which have anti-inflammatory and immunosuppressive actions, are considered to be an effective first-line treatment in children and adults with segmental or non-segmental vitiligo of recent onset (Abu Tahir et al., 2010; Gawkrodger et al., 2010), and, indeed, following treatment of vitiligo patients with systemic steroids, a reduction in anti-melanocyte antibody levels and in antibody-mediated anti-melanocyte cytotoxicity has been demonstrated (Hann et al., 1993; Takei et al., 1984).

Psoralen with ultraviolet radiation (PUVA) is used as a second-line therapy for vitiligo (Alomar, 2010; Gawkrodger et al., 2010). Following PUVA treatment, a reduction in the number of Langerhans cells and a decrease in the expression of vitiligo-associated melanocyte antigens, which could lead to a blocking of antibody-dependent cell-mediated cytotoxicity against melanocytes, have been noted in vitiligo patients (Kao & Yu, 1992; Viac et al., 1997). In addition, ultraviolet radiation can induce the expression of anti-inflammatory cytokines, modulate the expression of intercellular adhesion molecule-1, and induce apoptosis of skin-infiltrating T lymphocytes (Duthie et al., 1999; Krutmann & Morita, 1999).

2.6 Humoral immune responses

2.6.1 Melanocyte antibodies

Antibodies to melanocytes occur at a significantly increased frequency in the sera of vitiligo patients compared with healthy individuals (Cui et al., 1992; Cui et al., 1995; Farrokhi et al., 2005; Hann et al., 1996a; Hann et al., 1996b; Naughton et al., 1983a; Naughton et al., 1983b; Rocha et al., 2002). As well as circulating antibodies, antibody deposits have been noted in the basement membrane zones of depigmented areas in patients with vitiligo (Uda et al., 1984). However, no B cells or antibody has yet been isolated from vitiligo lesions. Interestingly, correlations can also exist between the incidence and level of melanocyte antibodies and both the activity and extent of vitiligo (Aronson & Hashimoto, 1987; Harning et al., 1991; Kemp et al., 2011; Naughton et al., 1986b; Yu et al., 1993), indicating that melanocyte antibodies are possible markers of disease progression.

Predominantly, melanocyte antibodies have been characterised as IgG (Cui et al., 1992; Cui et al., 1995; Farrokhi et al., 2005; Hann et al., 1996a; Hann et al., 1996b; Naughton et al., 1983a; Naughton et al., 1983b; Rocha et al., 2002; Uda et al., 1984) and as belonging to subclasses IgG1, IgG2 and IgG3 (Xie et al., 1991), although anti-melanocyte IgA antibodies have also been reported (Aronson & Hashimoto, 1987). Initial immunoprecipitation studies using melanoma cell extracts revealed that antibodies in vitiligo patients were most commonly directed against antigens with molecular weights of 35, 40-45, 75, 90 and 150 kDa (Cui et al., 1992). Several of the proteins (40-45, 75 and 150 kDa) appeared to be common tissue antigens, while others (35 and 90 kDa) were preferentially expressed on melanocytes (Cui et al., 1992). In immunoblotting studies with melanocyte extracts, antigens of 45, 65, and 110 kDa have been identified (Hann et al., 1996b; Park et al., 1996), while vitiligo-associated antibodies have been demonstrated to recognise melanoma cell proteins of 68, 70, 88, 90, 110 and 165 kDa (Hann et al., 1996a; Rocha et al., 2002).

The identity of several vitiligo-associated antibody targets has been reported and these are summarised in Table 3. Included are the melanogenic enzymes tyrosinase (Baharav et al., 1996; Kemp et al., 1997a; Song et al., 1994) and tyrosinase-related protein-2 (Kemp et al., 1997b; Okamoto et al., 1998), and the melanosomal matrix protein gp100 (Pmel17) (Kemp et al., 1998a). The technique of peptide phage-display has identified the melanin-concentrating hormone receptor 1 (MCHR1) and tyrosine hydroxylase as targets of vitiligo patient

antibodies (Kemp et al., 2002). Recent proteomic analysis has also revealed lamin A is a vitiligo-associated antigen (Li et al., 2010).

Antigen	Number of Patients with Antibodies (%)	Number of Controls with Antibodies (%)	Reference
Lamin A	24/84 (28.6)	2/64 (3.1)	Li et al., 2010
MCHR1	9/55 (16.4)	0/28 (0)	Kemp et al., 2002
MCHR1	12/84 (14.3)	Not reported	Li et al., 2010
Pmel17	3/53 (5.9)	0/20 (0)	Kemp et al., 1998a
SOX10	3/93 (3.2)	0/65 (0)	Hedstrand et al., 2001
SOX9	1/93 (1.1)	0/65 (0)	Hedstrand et al., 2001
Tyrosinase	16/26 (61)	0/31 (0)	Song et al., 1994
Tyrosinase	7/18 (39)	0/12 (0)	Baharav et al., 1996
Tyrosinase	5/46 (10.9)	0/20 (0)	Kemp et al., 1997a
TRP-1	3/53 (5.9)	0/20 (0)	Kemp et al., 1998b
TRP-1	8/84 (9.5)	Not reported	Li et al., 2010
TRP-2	3/53 (5.9)	0/20 (0)	Kemp et al., 1997b
TRP-2	10/15 (67)	0/21 (0)	Okamoto et al., 1998
TRP-2	20/30 (67)	1/35 (2)	Okamoto et al., 1998
Tyrosine hydroxylase	18/79 (23)	0/28 (0)	Kemp et al., 2011

Table 3. Defined antibody targets in patients with vitiligo

2.6.2 Pathogenic mechanisms

With respect to pathogenic effects, vitiligo-associated antibodies are able to destroy melanocytes and melanoma cells *in vitro* and *in vivo* by complement-mediated damage and antibody-dependent cellular cytotoxicity (Fishman et al., 1993; Gottumukkala et al., 2006; Norris et al., 1998a). Complement-mediated cytolysis of melanocytes by vitiligo patient antibodies appears to be cell selective and more common in individuals with active disease (Cui et al., 1993). Passive immunisation of nude mice grafted with human skin has also indicated that IgG from vitiligo patients can induce melanocyte destruction (Gilhar et al., 1995). Furthermore, IgG melanocyte antibodies from individuals with vitiligo can induce HLA-DR and intercellular adhesion molecule-1 expression on and release of interleukin-8 from melanocytes (Yi et al., 2000). Such changes that may enhance the antigen-presenting activity of melanocytes allowing antigen-specific immune effector cell attack resulting in melanocyte destruction.

Antibodies against MCHR1 have been shown to block the function of the receptor in a heterologous cell line (Gottumukkala et al., 2006). Stimulation of MCHR1 in cultured melanocytes with melanin-concentrating hormone (MCH) can down regulate the actions of α-melanocyte-stimulating hormone, including the production of melanin, suggesting that the MCH/MCHR1 signalling pathway has a role with the melanocortins in regulating melanocyte function (Hoogduijn et al., 2002). Any adverse effects of MCHR1 antibodies upon the functioning of the receptor in melanocytes could potentially disrupt normal melanocyte behaviour, a feature that could precede the clinical manifestation of vitiligo. However, this has not yet been reported and is still the object of study. More recent work

has found that 69% (9/13) of vitiligo patient sera tested induced melanocyte detachment in a reconstructed epidermis model, although this was unrelated to either the extent or the activity of the disease (Cario-Andre et al., 2007). Further studies are needed to confirm that this serum effect is antibody mediated and, if so, that the antibody activity is specific to vitiligo patient sera.

2.6.3 Other antibodies

Circulating organ-specific autoantibodies, particularly to the thyroid, adrenal glands, gastric parietal cells, and pancreatic islet cells are commonly detected in the sera of vitiligo patients (Brostoff, 1969; Betterle et al., 1976; Mandry et al., 1996; Zauli et al., 1986). Moreover, antinuclear antibody and IgM-rheumatoid factor have been detected at a significant frequency in vitiligo patients (Farrokhi et al., 2005). Anti-keratinocyte intracellular antibodies that correlate with disease extent and activity have also been detected in vitiligo patients (Yu et al., 1993).

2.7 Cellular immune responses

2.7.1 Cytokines

An imbalance of cytokines, which can affect melanocyte activity and survival, has been shown in vitiligo lesional skin (Moretti et al., 2002). The level of granulocyte-macrophage colony-stimulating factor is reduced in patients with active vitiligo compared with healthy controls (Yu et al., 1997; Moretti et al., 2002). This cytokine has been found to act as a growth factor for melanocytes and a decrease in its production slows down the proliferation of surviving melanocytes in vitiligo lesions (Imokawa et al., 1996). Other melanogenic cytokines, including stem cell factor and endothelin-1, are also lowered in depigmented lesions (Moretti et al., 2002).

Serum levels of soluble interleukin-2 receptor can be used to monitor *in vivo* immune activation, and its elevation has been correlated with T cell-mediated immune disease. Indeed, the level of the soluble interleukin-2 receptor level in vitiligo patients is significantly increased compared with that of controls, indicating that the activation of T cells is a component in the pathogenesis of vitiligo (Tu et al., 1999; Yeo et al., 1999). The production of interleukin-6 by mononuclear cells is also elevated in vitiligo patients (Yu et al., 1997). This cytokine can induce the expression of intercellular adhesion molecule-1 on melanocytes thereby facilitating leukocyte-melanocyte interactions and consequently cause immunological damage (Kirnbauer et al., 1992). Increased production of interleukin-8, which can attract neutrophils to vitiligo lesions amplifying destructive inflammatory reactions, has also been reported in the mononuclear cells of vitiligo patients (Yu et al., 1997). Furthermore, the expression of tumour necrosis factor-alpha, an inflammatory mediator involved in the pathogenesis of autoimmune disease, is significantly elevated in vitiligo skin (Moretti et al., 2002). However, the exact roles in vitiligo pathogenesis of these inflammatory cytokines, which can also act as paracrine inhibitors of melanocyte proliferation and of melanogenesis, remain to be determined.

2.7.2 Macrophages

Macrophage infiltration has been demonstrated in vitiligo lesions, with increased numbers present in perilesional skin (Le Poole et al., 1996; Van den Wijngaard et al., 2000). It is possible that macrophages are involved in clearing melanocytes that have been induced to

apoptose by cytotoxic T lymphocytes. Additional evidence for the active involvement of macrophages in vitiligo pathogenesis is demonstrated by their expression of immunoglobulin receptors: in a mouse model, it has been shown that macrophages, expressing the common gamma chain of the activating Fc gamma receptors, can mediate vitiligo in the presence and absence of complement C3 fraction (Trcka et al., 2002)

2.7.3 Dendritic cells

The density of Langerhans cells in vitiliginous skin has been variously reported as normal, increased and decreased compared with pigmented skin from the same patients and from control subjects (Claudy & Rouchouse, 1984; Hatchcome et al., 1987; Riley, 1967; Searle et al., 1991). The differences in the documented Langerhans cells densities may be due to the type of vitiligo, the sampling techniques used or the site of skin biopsies. An increase in the number of Langerhans cells could contribute to the immunological processes that damage melanocytes. However, although degenerative changes in Langerhans cells have been observed in vitiligo skin lesions, their role in vitiligo still remains unclear. More recently, dendritic cell-mediated destruction of melanocytes has been demonstrated *in vivo* and *in vitro* (Kroll et al., 2005). This process is related to the release of heat-shock protein 70 by stressed melanocytes, which induces an immune response against the cells from which it is produced, and to the increased expression of tumour-necrosis factor-related apoptosis inducing ligand receptors on stressed melanocytes making them more prone to killing by dendritic cells (Denman et al., 2008; Kroll et al., 2005).

2.7.4 T cells

Autoimmune disorders are often associated with an expansion of peripheral helper T cells. However, with respect to vitiligo, inconsistent data regarding abnormalities in circulating helper T cells have been reported. An increase in the number of activated helper T cells was detected in patients with stable vitiligo as well as in their first-degree relatives when compared with healthy individuals (Abdel-Naser et al., 1992; D'Amelio et al., 1990; Soubiran et al., 1985). In contrast, a decrease in the helper T cell population has also been observed in individuals with vitiligo (Grimes et al., 1986; Halder et al., 1986). No simple explanation exists for these differences but they could be attributable to the factors such as the population of patients under study, disease characteristics and received treatments.

Circulating melanocyte-specific cytotoxic T lymphocytes that target melanocyte-specific antigens, including Melan-A (MART-1), gp100 (Pmel17) and tyrosinase, have been detected in vitiligo patients (Lang et al., 2001; Ogg et al., 1998; Palermo et al., 2001). They express high levels of the skin-homing receptor cutaneous lymphocyte-associated antigen and their frequency correlates with both the extent and activity of the disease (Lang et al., 2001). In addition, melanocyte-specific T cells have cytotoxic reactivity towards melanocytes (Ogg et al., 1998). Such findings are consistent with a role for skin-homing, autoreactive, melanocyte-specific T cells in causing the destruction of melanocytes in vitiligo.

Histological studies of skin biopsies from vitiligo patients have demonstrated that infiltrating cytotoxic and helper T cells are most prominent at the periphery of vitiligo lesions (Al Badri et al., 1993b; Van den Wijngaard et al., 2000). Many of the inflammatory cells are activated, as indicated by the expression of the MHC class II antigen HLA-DR, and a significant number also exhibit high levels of the receptor cutaneous lymphocyte-associated antigen, typical of skin-homing T cells (Al Badri et al., 1993b; Van den Wijngaard

et al., 2000). Local activation of cytotoxic T cells at the perilesional epidermal/dermal junction of vitiliginous skin is also suggested by the presence of granzyme B+ and perforin+ cells (Van den Wijngaard, et al., 2000). There is evidence for interleukin-2 receptor and interferon-gamma receptor expression by the lymphocytic infiltrate (Abdel-Naser et al., 1994), and also for down-regulation of the helper T cell 2-dependent CDw60 molecule in the vitiliginous epidermis suggesting that infiltrating T cells may exhibit a helper T cell 1-type cytokine production pattern which is consistent with cell-mediated organ-specific autoimmunity (Le Poole et al., 2003). In addition, perilesional T cell clones exhibit a predominant type-1-like cytokine secretion profile (Wankowicz-Kalinska et al., 2003). More recently it has been demonstrated that T lymphocytes obtained from perilesional skin biopsies are enriched for cytotoxic T cells that recognise melanocyte antigens tyrosinase, gp100 and MelanA (Van den Boorn et al., 2009). Moreover, upon infiltration of autologous pigmented skin, isolated perilesional T lymphocytes efficiently kill melanocytes, providing direct evidence that cytotoxic T cells can cause the depigmentation seen in vitiligo (Van den Boorn et al., 2009). Additional to this, are findings that regulatory T cells occur at a reduced level in the skin of vitiligo patients (Klarquist et al., 2010). This may allow the unchecked destruction of melanocytes by cytotoxic T cells in vitiligo lesions (Klarquist et al., 2010).

3. Conclusion

Autoimmunity is one hypothesis forwarded to explain the development of vitiligo due to the evidence presented in this review. However, it is most likely that interacting mechanisms, of which immune responses are a part, are responsible for the clinical manifestations of the disease (Le Poole et al., 1993a). In addition, although the evidence for the role of immune-related genes in the aetiology of vitiligo is clear, the limited concordance in identical twins (Alkhateeb et al., 2003) indicates that other factors, probably environmental, are also involved in its development, making the disease complex, polygenic, and multi-factorial. Notably, *in vitro* studies have provided a link and a temporal sequence connecting cellular oxidative stress (Dell'Anna & Picardo, 2006; Schallreuter et al., 1991; Schallreuter et al., 2001; Schallreuter et al., 2005) 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 melanocytes (Kroll et al., 2005). This work suggests that intrinsic damage to melanocytes could be the initiating event in vitiligo development followed by a secondary immune response by cytotoxic T cells which exacerbates the destruction of melanocytes and progresses the disease (Hariharan et al., 2010; Le Poole & Luiten, 2008; Van den Boorn et al., 2011). Indeed, 50% of vitiligo patients experience a Koebner phenomenon, whereby depigmented lesions develop at a site previously exposed to a physical stress (Le Poole & Luiten, 2008).

As indicated, it is most likely that immune responses in vitiligo are of a secondary nature following melanocyte damage. Indeed, several vitiligo-associated autoantigens such as tyrosinase and gp100 are located intracellularly, and it has been suggested that either the formation of neo-antigens due to haptenation, the exposure of cryptic epitopes or the modification of proteins during apoptosis could account for immune responses to these molecules (Namazi, 2007; Westerhof & d'Ischia, 2007). Following processing by mature Langerhans cells, antigenic peptides could be presented to T cells which have escaped clonal deletion or to naïve T lymphocytes which have not been tolerised against cryptic epitopes (Namazi, 2007; Westerhof & d'Ischia, 2007). Antibodies could then be produced following

the stimulation of B lymphocytes by activated helper T cells (Namazi, 2007), and activated cytotoxic T cells could directly attack melanocytes expressing antigenic peptides on their surface in the context MHC class I molecules (Hedley et al., 1998; Le Poole et al., 1993b). In the case of immune reactivities against common cellular antigens, the selective destruction of melanocytes in vitiligo might occur because they are intrinsically more sensitive to immune-mediated injury than other skin cells (Norris et al., 1988b).

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