Immunological pathomechanisms in vitiligo

E. Helen Kemp, Elizabeth A. Waterman and Anthony P. Weetman

Vitiligo is a depigmenting disorder characterised by the loss of melanocytes from the cutaneous epidermis. Although the exact aetiology of vitiligo has not yet been established, the abnormal immune responses frequently observed in vitiligo patients have led to the suggestion that, in some cases, the condition has an autoimmune component. Briefly, circulating autoantibodies and autoreactive T cells that recognise pigment cell antigens have been detected in the sera of a significant proportion of vitiligo patients compared with healthy individuals. In addition, vitiligo is often associated with other disorders that have an autoimmune origin, including Hashimoto's thyroiditis, Graves' disease, type 1 insulin-dependent diabetes mellitus and Addison's disease. Furthermore, effective use of immunosuppressive therapies to treat vitiligo, the association of vitiligo with certain major histocompatibility complex antigens, and evidence from animal models of the disease have all added credence to the hypothesis that immune reactions play a role in vitiligo pathogenesis. This review presents and discusses the evidence for immunological pathomechanisms in vitiligo.

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The cutaneous melanocyte is the skin cell responsible for the production of the pigment melanin from tyrosine, a process referred to as melanogenesis. This is a complex biochemical synthesis that is regulated by enzymes such as tyrosinase, tyrosinase-related protein 1 (TRP1) and tyrosinase-related protein 2 (TRP2), and that occurs in membrane-bound organelles termed melanosomes (pigment granules) (Refs 1, 2). One important role of melanin is the absorption of harmful incident ultraviolet radiation to protect the genome of epidermal melanocytes and keratinocytes from damage.

Vitiligo is an acquired hypomelanotic disorder characterised by circumscribed depigmented macules or patches resulting from the loss of functional melanocytes and of melanin from the epidermis (Fig. 1). Large population surveys have shown a prevalence ranging from 0.38 to 1.13% (Refs 3, 4), and in 50% of cases the condition begins before the age of 20 years (Ref. 5). More women than men are referred with vitiligo, although the incidence of the disorder is not believed to be sex-linked. Familial cases of vitiligo are common, indicating a hereditary factor: between 6 and 38% of vitiligo patients have family members with the disease (Ref. 6). However, vitiligo is not transmitted by a simple mendelian mechanism and its inheritance pattern is more consistent with that of a polygenic trait (Ref. 5). Although, at first, vitiligo might be viewed as a minor disorder, the impact on patients' self-esteem and social interactions can be devastating (Refs 7, 8), particularly in patients with deeply pigmented skin.

Many possible causes of vitiligo have been proposed, including stress, infections, mutations, neural factors, melatonin receptor dysfunction, and impaired melanocyte migration and/or proliferation. In addition, the accumulation of toxic intermediate products of melanin synthesis (Refs 9, 10), the breakdown of free radical defence (Ref. 11) and the build-up of excessive quantities of hydrogen peroxide (Refs 12, 13) have all been suggested to result in the self-destruction of pigment cells. An autoimmune aetiology has also been proposed, and this is supported by the frequent association of vitiligo with autoimmune diseases (Refs 14, 15), together with studies demonstrating that many vitiligo patients have autoantibodies and autoreactive T cells against melanocyte antigens (Refs 16, 17). It is possible that these different causal factors can act independently or together to yield the same effect – namely, the disappearance of melanocytes from the skin (Ref. 18). For example, autoimmunity might arise as a secondary phenomenon following the auto-destruction of

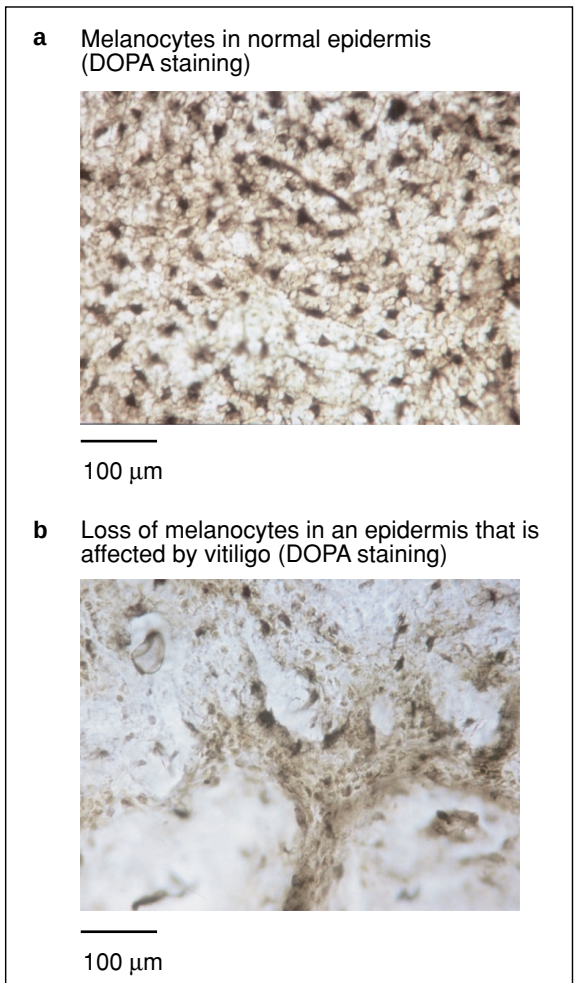

Figure 1. Loss of melanocytes in epidermis affected by vitiligo. (a) Melanocytes in a sheet of normal epidermis shown by dihydroxyphenylalanine (DOPA) staining, which detects the activity of the melanogenic enzyme tyrosinase present in melanocytes. (b) Appearance of an epidermal sheet from a patient who has vitiligo, after staining with DOPA, showing a much reduced melanocyte density. Images courtesy of Dr D.J. Gawkrodger, Department of Dermatology, Royal Hallamshire Hospital, Sheffield, UK **(fig001hks)**.

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melanocytes resulting from the factors described above. This might then amplify the damage to pigment cells. Moreover, several clinical types of vitiligo (e.g. generalised, segmental, focal; see Box 1) are recognised (Ref. 19), and different pathogenic mechanisms could account for these subsets. Indeed, autoimmunity is more common in patients who have non-segmental vitiligo compared with those who have the segmental/focal form of the disease (Ref. 20). This article focuses on the immunological mechanisms that might play a part in the aetiology of vitiligo.

Clinical features of and therapies for vitiligo

Vitiligo is most often classified clinically according to the extent and distribution of depigmentation, as summarised in Box 1 (Refs 20, 21, 22). It has been proposed that the segmental and focal presentations of the disease constitute a separate subgroup to the non-segmental forms of vitiligo (Ref. 20) because, compared with focal and segmental vitiligo, non-segmental forms show a later age of onset, a stronger association with autoimmunity and unstable results following autologous grafting.

Therapies for vitiligo can be categorised as medical or surgical, and these are summarised in Table 1. Their use and efficacy have been extensively reviewed elsewhere (Refs 19, 21, 22). In addition, an important part of the management of vitiligo is psychological support, because psychological damage is one of the basic aspects of the disease that needs to be addressed.

Box 1. Clinical presentations of vitiligo

Segmental/unilateral
Segmental vitiligo often presents in childhood and occurs in a dermatomal, asymmetric distribution with one or more macules localised to one area of the body. It is rarely associated with autoimmune disorders and responds well to autologous grafting.

Focal
Focal vitiligo describes one or more depigmented patches localised in a discrete area with a non-dermatomal distribution.

Symmetrical/bilateral
This is the most common type of vitiligo and is often referred to as generalised. It is characterised by a bilateral, symmetrical depigmentation with a widespread distribution of many macules in a random pattern (Fig. 2). Many parts of the body can be affected, including the face (particularly periorificial areas), the neck, torso, hands and legs. A later age of onset is normal for this clinical subclass and it is associated more often with autoimmunity. Unstable results are evident following autologous grafting in patients with this type of vitiligo.

Acrofacial
Vitiligo of this type is characterised by depigmentation of the distal fingers and facial orifices – the latter in a circumferential pattern. It often forms with symmetrical vitiligo.

Universal
This type of vitiligo is characterised by the loss of pigmentation over the entire body, but is rare.

Inflammatory
Cases of inflammatory vitiligo are rare, but are characterised by pruritus (itching) and erythema (reddening of the skin) at the periphery of active, depigmenting lesions.

Trichrome
In trichrome vitiligo, the lesions have a complex outline and, as they progress, fuse with neighbouring macules to form a complex pattern. Within each lesion, the loss of pigment might be partial or complete, or there can be both partial and complete depigmentation in the same area.

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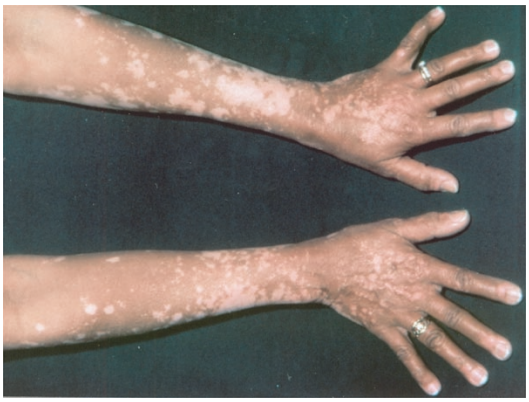

Bilateral symmetrical vitiligo on the dorsal aspects of the hands

Figure 2. Bilateral symmetrical vitiligo on the dorsal aspects of the hands. Image courtesy of Dr D.J. Gawkrodger, Department of Dermatology, Royal Hallamshire Hospital, Sheffield, UK **(fig002hks)**.

Table 1. Therapies for vitiligo (tab001hks)

Medical treatments	Refs
Cosmetic modalities	22
Corticosteroids (topical or systemic)	19, 21, 22
Psoralen (topical or systemic) and ultraviolet A	19, 21, 22
Khellin (topical or systemic) with ultraviolet A or natural sunlight	21
Phenylalanine (topical or systemic) with ultraviolet A	22
Topical pseudocatalase with ultraviolet B	21
Oral antioxidants (e.g. vitamin E acetate; selenio-methionine)	21
5-Fluorouracil (topical)	22
Depigmentation with monobenzyl ether of hydroquinone	22
Surgical treatments	
Epidermal grafting	19, 22
Autologous minigrafts	19, 22
Transplantation of cultured epidermis	19, 22
Transplantation of non-cultured melanocytes	19, 22
Tattooing	19

The role of immunological responses in vitiligo

In this section, the evidence for immunological responses playing a role in the aetiology of vitiligo is presented and discussed. Possible cellular and humoral mechanisms of vitiligo aetiopathogenesis are summarised in Figure 3.

The association of vitiligo with autoimmune disorders

In some patients, vitiligo is associated with disorders that are considered to have an autoimmune origin (Table 2). These include autoimmune thyroid disease (Ref. 14), insulin-dependent diabetes mellitus (IDDM) (Ref. 15), alopecia areata (Ref. 23), pernicious anaemia (Ref. 24), Addison's disease (Ref. 25) and autoimmune polyendocrine syndromes (Refs 26, 27). Vitiligo patients are also more likely to suffer from autoimmune disease. Autoimmune thyroiditis, for example, has a prevalence of up to 30% in patients with vitiligo (Ref. 28), a figure that is significantly higher than the 1% frequency of autoimmune thyroid disease in the general population (Ref. 29). Autoimmune gastritis, pernicious anaemia, alopecia areata and IDDM are also found more commonly in vitiligo patients compared with normal subjects, with frequencies of 15%, 5.3%, 16% and 7.2%, respectively (Refs 28, 30). These associations suggest that, in some patients, autoimmune responses might have a role in the pathogenesis of vitiligo.

Systemic disorders in vitiligo

Although loss of melanocytes from the skin is almost always the primary and initial symptom in vitiligo, other pigment cells in the body can be affected. Melanocytes are located in the inner ear (Ref. 31) and vitiligo-associated auditory problems have been reported in some patients (Refs 32, 33, 34). Damage can also occur to melanocytes within the eye. Indeed, ocular disorders of the uveal tract, including both iris and conjunctival depigmentation, chorioretinal

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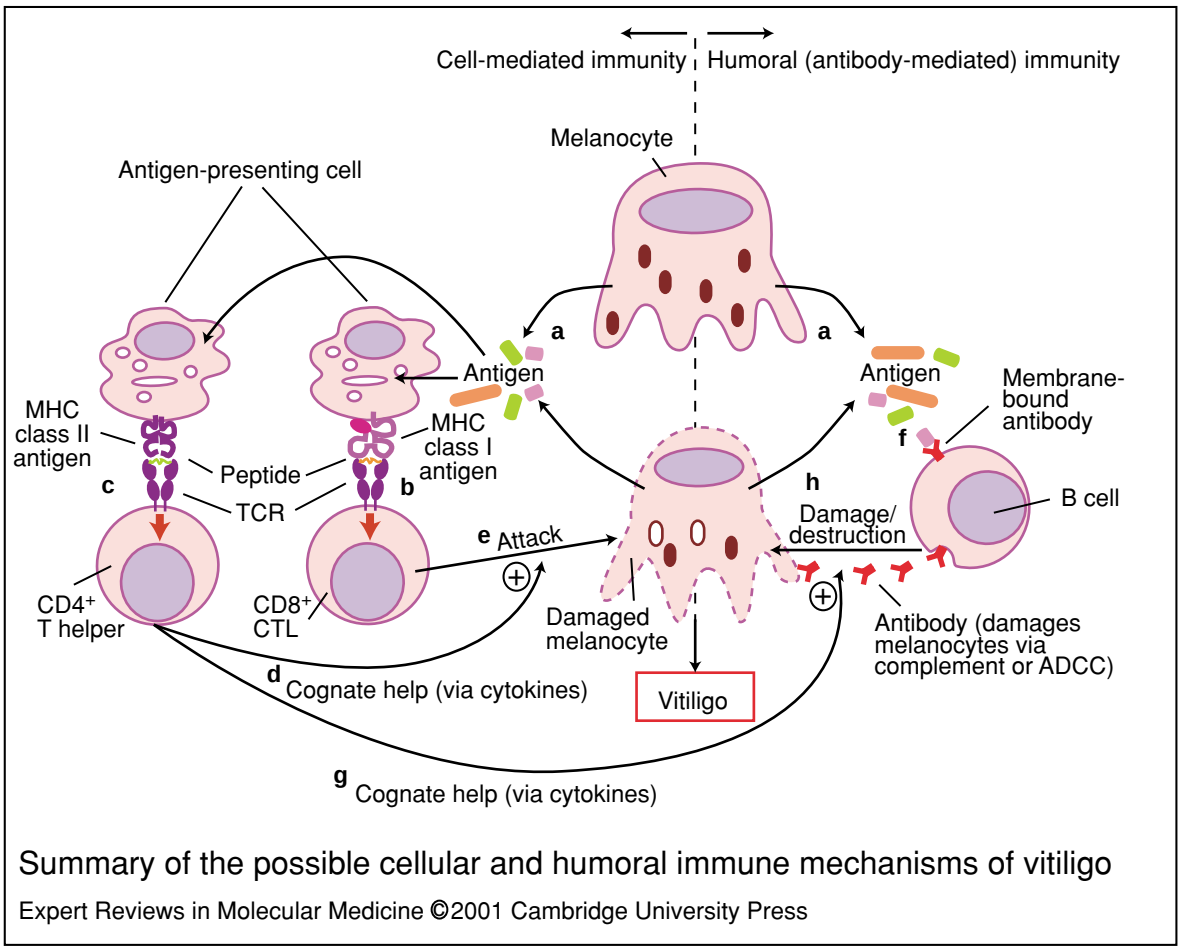

Summary of the possible cellular and humoral immune mechanisms of vitiligo

Figure 3. Summary of the possible cellular and humoral immune mechanisms of vitiligo. (a) Antigens produced by melanocytes (including those released from damaged melanocytes) can be recognised by antigen-specific immune effector cells including cytotoxic T cells, T helper cells and B cells. Recognition of melanocyte antigens might also arise through crossreaction from immune responses to other cell types or infectious agents (not shown). (b) In cell-mediated immunity, after processing of antigens by antigen-presenting cells, antigenic peptides are presented to the T-cell receptors (TCR) of cytotoxic T lymphocytes (CTLs) in the context of major histocompatibility complex (MHC) class I molecules. (c, d) Cognate help (via cytokine production) by antigen-specific T helper cells, in the context of antigenic peptides presented on MHC class II molecules, is required for (e) a long-lasting cytotoxic T-cell response against melanocytes that can lead to their destruction. (f) In humoral immunity, antigens are captured by the antigen-specific membrane immunoglobulins of B cells. The production and secretion of antigen-specific antibodies by B cells are also dependent on (g) cognate help (via cytokine production) by antigen-specific T helper cells. (h) Anti-melanocyte antibodies can destroy pigment cells by either antibody-dependent complement-mediated damage or antibody-dependent cell-mediated cytotoxicity (ADCC) **(fig003hks)**.

depigmentation and uveitis, as well as abnormalities of the retinal pigment epithelium such as retinitis pigmentosa, have been found at a higher incidence in vitiligo patients (Refs 35, 36, 37). That extracutaneous melanocytes can be affected in some vitiligo patients suggests that systemic immunological reactions directed at pigment cells might play a part in the development of the disease.

Response of vitiligo to immunosuppressive therapies

Several reasonably effective therapies for vitiligo (Table 1), including psoralen with ultraviolet A radiation (PUVA) (Ref. 38), topical corticosteroids (Ref. 39) and topical cytotoxic drugs such as fluorouracil (Ref. 40), are immunosuppressive in their mode of action. Repigmentation following treatment is suggested to result from the

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Table 2. Association of vitiligo with autoimmune disorders (tab002hks)

Autoimmune disease	Number of patients in study	Percentage with vitiligo	Ref.
Autoimmune polyglandular syndrome type 1	71	8	26
Autoimmune polyglandular syndrome type 1	68	13	27
Autoimmune polyglandular syndrome type 2	224	5	26
Autoimmune polyglandular syndrome type 2	22	4.5	27
Pernicious anaemia	125	9	24
Insulin-dependent diabetes mellitus (juvenile)	300	1.7	15
Autoimmune thyroid disease (Graves' disease)	90	7	14
Alopecia areata	808	1.8	23

suppression of the local immune reactions responsible for damaging pigment cells. This therapeutic response to immunosuppression implies the involvement of immunological pathomechanisms in vitiligo.

Immunogenetic factors

Certain major histocompatibility complex (MHC) antigens, polymorphisms of the cytotoxic T lymphocyte antigen 4 (CTLA-4) gene and mutations in the autoimmune regulator (AIRE) gene have all been associated with the development of autoimmune disorders that result from aberrant immunological responses. In some vitiligo patients, a genetic predisposition to autoimmunity, resulting in the production of abnormal immune reactions to melanocytes or to other cells, might be a primary cause of the disease.

MHC molecules

All known autoimmune endocrinopathies are associated with certain MHC class II human leukocyte antigen (HLA)-DR alleles (Refs 41, 42, 43), and a similar association in vitiligo would be indirect evidence that it too might have an autoimmune basis. The studies carried out so far with respect to vitiligo (Refs 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55) are summarised in Table 3. Although these show variability, the significant association of allele HLA-DR4 and vitiligo has been reported for several different populations (Refs 46, 50, 51). The exact molecular basis underlying the association of autoimmunity with particular HLA specificities remains to be determined.

Several autoimmune disorders are associated with homozygous or heterozygous deficiencies of the complement components C4 and C2 (MHC class III molecules) (Ref. 56). In vitiligo patients, an increased frequency of heterozygous C4 and C2 deficiency has been reported (Ref. 46), but exactly what role this plays in the development of vitiligo is unknown.

CTLA-4

CTLA-4 is a T-cell surface molecule (Ref. 57) that is involved in the control of T-cell apoptosis (cell death) (Ref. 58) and in the negative regulation of T-cell activation (Ref. 59). It is therefore a candidate gene for contributing to the development of T-cell-mediated autoimmune disease if its expression or function is adversely affected by detrimental mutations and/or polymorphic alleles. Indeed, several CTLA-4 gene polymorphisms (Ref. 60), which might affect the expression or the functioning of the protein, are associated with autoimmune disorders such as Graves' disease (Ref. 61), autoimmune hypothyroidism (Ref. 61) and autoimmune Addison's disease (Ref. 62). Certain of these polymorphic markers have also been associated with vitiligo (Refs 63, 64), suggesting that the disorder might occur in some individuals because of a genetic predisposition to the development of autoimmunity. As yet, the molecular basis

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Table 3. Major histocompatibility complex antigen associations with vitiligo (tab003hks)

Origin	Number of patients in study	Associated specificity	Ref.
Slovakia	67	A2, Dw7	44
Italy	87	A30, B27, Cw6, DQw3	45
Holland	42	DR4, C4BQ0	46
Kuwait	40	B21, Cw6	47
Oman	50	Bw6, DR7	48
Hungary	88	DR1, DR3	49
America (African)	24	DR4, DQw3	50
America (Caucasian)	48	DR4	51
Italy (Northern)	86	A3	52
Italy (Northern)	93	A30, Cw6, DQw3	54
Morocco (Jewish)	18	B13	53
Yemen	16	Bw35	53
Germany (Northern)	102	A2	55

for the association of particular CTLA-4 polymorphisms with autoimmune disorders has not been established.

AIRE

Vitiligo is a common manifestation of autoimmune polyglandular syndrome type 1 (Ref. 27), a disease that is most consistently characterised by the development of mucocutaneous candidiasis, Addison's disease and hypoparathyroidism. This disorder is caused by mutations in the AIRE gene (Refs 65, 66), which is normally expressed in immune-related organs such as the thymus and lymph nodes. The AIRE protein is predicted to act as a transcription factor (Refs 65, 66), although this has yet to be verified. Autoimmune polyglandular syndrome type 1 and associated vitiligo are proposed to be a consequence of immune dysregulation resulting from mutations in AIRE that affect the functioning of the protein. However, this needs to be confirmed. The AIRE gene is unlikely to play a role in the development of vitiligo that is not associated with autoimmune polyglandular syndrome type 1.

Animal models of vitiligo

The study of animal models has added credence to the theory that immune mechanisms might play a part in the development of vitiligo. Several spontaneous animal models of vitiligo exist (Ref. 67), although the exact relevance of such models to the equivalent human disorder remains to be established. The well-documented Smyth chickens (Ref. 68) express a genetically inherited form of vitiligo-like depigmentation resulting from the loss of melanocytes in feather and ocular tissues. In this avian model, vitiligo begins with an inherent melanocyte defect (Ref. 69), which is followed by an autoimmune response involving both humoral and cellular reactions that eliminate abnormal pigment cells (Refs 69, 70, 71, 72). 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 (Refs 73, 74). Autoantibodies to chicken melanocytes have also been detected in the sera of 100% of Smyth chicks but not in the sera of normally pigmented birds (Ref. 75). These antibodies were found to be present both

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before and during the presentation of vitiligo (Ref. 76). In mammalian melanocytes, the primary target antigen of these autoantibodies has been identified as the melanogenic enzyme TRP1 (see below) (Ref. 77). Other animal models of vitiligo, including horses, cats and dogs, also show anti-pigment-cell antibodies (Ref. 78), which recognise a similar pattern of melanocyte antigens as antibodies from human vitiligo patients in immunoprecipitation experiments (Ref. 16); this indicates that similar immunological responses might occur in animals and humans.

Cell-mediated immune responses in vitiligo

Peripheral T cells

Autoimmune disorders are often associated with an expansion of peripheral $CD4^+$ T cells (Ref. 79). However, with respect to vitiligo, inconsistent data regarding abnormalities in circulating T cells have been reported. An increase in the number of $CD4^+$ T cells and an elevated $CD4^+/CD8^+$ ratio have been detected in patients with stable vitiligo and in their first-degree relatives (Refs 46, 80, 81). A higher proportion of activated peripheral T cells, as determined by the expression of HLA-DR, has also been found in vitiligo patients compared with healthy individuals (Ref. 82). By contrast, a decrease in the $CD4^+$ T-cell population along with a reduced $CD4^+/CD8^+$ ratio have also been observed (Refs 83, 84). No simple explanation exists for these differences.

A recent study demonstrated the presence of circulating cytotoxic T lymphocytes (CTLs) specific for MelanA (a melanocyte-specific protein of unknown function) and tyrosinase in a significant number of vitiligo patients when compared with control subjects (Ref. 85). The T cells expressed high levels of the skin-homing receptor cutaneous lymphocyte-associated (CLA) antigen and their frequency correlated with extent of depigmentation. These findings are consistent with a role for skin-homing, autoreative, melanocyte-specific T cells in causing the destruction of pigment cells in vitiligo, and this study is the first to identify a cellular immune response to melanocyte-specific antigens in this depigmenting disorder.

T cells in vitiligo lesions

Histological studies of skin biopsies from vitiligo patients have shown that inflammatory cells are most prominent at the periphery of vitiligo lesions (i.e. perilesional) (Ref. 86). The dermal and epidermal infiltrate consists of $CD3^+$, $CD4^+$ and $CD8^+$ T cells that are closely associated with the areas of melanocyte depletion (Refs 86, 87). Expression of the MHC class II antigen HLA-DR demonstrates that many of the infitrating T cells are activated (Refs 86, 87), and a significant number of T cells at the margins of vitiligo lesions also exhibit high levels of the CLA antigen, typical of skin-homing T cells (Refs 86, 87). In addition, there is evidence for interleukin 2 receptor (IL-2R) and interferon γ receptor (IFN-γR) expression by the lymphocytic infiltrate (Ref. 88). In rare cases of inflammatory vitiligo, similar observations with regard to perilesional, epidermis-infiltrating T cells have been made (Ref. 89). A recent study reported the presence of MelanA-specific $CD8^+$ CTLs, which also express CLA antigen, in cell lines derived from perilesional skin biopsies (Ref. 87). This is the first report of T-cell reactivity in vitiligo lesions being directed to a melanocyte-specific antigen. Overall, although these findings do not differentiate between whether the immune infiltrates are a result or a cause of the disease process, the results are suggestive of the involvement of local immune reactivity in melanocyte destruction.

How could aberrant T-cell reactivities arise and cause vitiligo?

The exact role of T-cell responses in the aetiology of vitiligo has yet to be established. In some patients, a genetic predisposition to immune dysregulation (see earlier) might be the initial causative factor leading to aberrant T-cell reactivities that destroy melanocytes. Alternatively, autoreactive T cells could arise in response to a challenge to the immune system. For example, antigens released from pigment cells disrupted by non-immune mechanisms could lead to the production of T cells that target melanocytes and, in turn, exacerbate the disorder. Pigment cells might also come under attack from cellular immune responses if they expose antigens that are similar to either an infectious agent (molecular mimicry) or other cells that are themselves the primary target of the autoreactive T cells. Which, if any, of these possibilities is the case remains open to speculation.

Cytokines

Many of the functions of immune cells are mediated through cytokines, and several studies

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have analysed the presence of these molecules in vitiligo patients. Serum levels of soluble IL-2R can be used to monitor in vivo immune activation, and elevated levels have been correlated with T-cell-mediated immune disease. Indeed, the level of soluble IL-2R in vitiligo patients is significantly increased compared with that of controls, indicating that the activation of T cells might be a component in the pathogenesis of vitiligo (Refs 90, 91). The production of IL-6 by mononuclear cells is also elevated in vitiligo patients (Ref. 92). This cytokine can induce the expression of intercellular adhesion molecule 1 (ICAM-1) on melanocytes (Ref. 93), which might then facilitate leukocyte–melanocyte interactions, leading to immunological damage of the pigment cells. Increased production of IL-8 from the mononuclear cells of vitiligo patients has also been reported (Ref. 92). IL-8 might attract neutrophils to vitiligo lesions, which could lead to the amplification of inflammatory reactions and the destruction of melanocytes.

The level of granulocyte–macrophage colony-stimulating factor (GM-CSF) made by mononuclear cells is reduced in patients with active vitiligo compared with healthy controls (Ref. 92). This cytokine has been found to act as a growth factor for melanocytes (Ref. 94) and a decrease in its production might slow down the proliferation of surviving melanocytes in vitiligo lesions. Although evidence implicates tumour necrosis factor (TNF) as a pathogenic component in autoimmune disease (Ref. 95), the production of this inflammatory mediator by mononuclear cells is decreased in patients with active vitiligo (Ref. 92).

Macrophages

Macrophage infiltration has been demonstrated in vitiligo lesions, with increased numbers present in perilesional skin (Ref. 87). It is possible that macrophages are involved in clearing melanocytes that have been induced to apoptose by CTLs (Ref. 87).

Langerhans cells

The density of Langerhans cells in vitiliginous skin has been variously reported as normal (Ref. 96), increased (Ref. 97) and decreased (Ref. 87) compared with pigmented skin from the same patients and from control subjects. Because Langerhans cells are active in presenting antigens to primed T cells in the epidermis, any increase in their numbers might contribute to the immunological processes that damage melanocytes in vitiligo lesions.

Abnormalities of vitiligo melanocytes

Recent studies have shown both abnormal expression of the MHC class II antigen HLA-DR and increased expression of ICAM-1 by perilesional melanocytes in vitiligo compared with pigment cells from normal skin (Refs 87, 98). Because these molecules have important roles in normal antigen presentation and in the activation of T helper cells, their expression by melanocytes might contribute to the abnormal cellular immune responses seen in vitiligo. The underlying cause of the molecular changes seen in perilesional melanocytes is not understood, but similar abnormal expression of HLA-DR and ICAM-1 is exhibited by thyroid follicular cells in autoimmune thyroid disease (Ref. 99), a disorder with which vitiligo is often associated. Macrophage markers CD68 and CD36 are also expressed on pigment cells in perilesional biopsies (Ref. 87), and both vitiligo and normal melanocytes are capable of expressing MHC class I molecules, which might allow interaction with CTLs (Ref. 100). Interestingly, normal melanocytes have also been reported to act as antigen-presenting cells (Ref. 101).

Humoral immunity in vitiligo

Anti-melanocyte antibodies

Significantly, antibodies to melanocyte antigens are present in the circulation of many patients with the disease (Ref. 16). In one study, 12/12 of vitiligo patients and 0/12 of control subjects were found to have anti-pigment-cell antibodies in their sera (Ref. 102). A correlation has been described between the incidence and level of melanocyte antibodies and disease activity in vitiligo: 8/10 patients with active vitiligo, 0/14 with inactive disease and 0/19 controls were found to have circulating anti-pigment-cell antibodies (Ref. 103). In addition, the presence of these antibodies is related to the extent of disease: they were detected in 50% of patients with minimal vitiligo (<2% of skin area involved) compared with 93% of patients with greater depigmentation (5–10% of skin area involved) (Ref. 104). Furthermore, vitiligo autoantibodies have the capacity to injure pigment cells: vitiligo antibodies are able to destroy melanocytes in vitro by complement-mediated damage and antibody-dependent

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cellular cytotoxicity (Ref. 105), and in vivo following passive immunisation of nude mice grafted with human skin (Ref. 106).

Vitiligo antibodies are usually directed against pigment cell antigens of 35 kDa, 40–45 kDa, 75 kDa, 90 kDa and 150 kDa, which are located on the surface of the cell (Refs 107, 108). Although the proteins have not been specifically identified, some (40–45 kDa, 75 kDa and 150 kDa) appear to be common tissue antigens, while others (35 kDa and 90 kDa) are preferentially expressed on pigment cells (Ref. 105). In addition, antibodies to the melanocyte-specific proteins tyrosinase (Refs 109, 110, 111), TRP1 (Ref. 112), TRP2 (Refs 113, 114) and Pmel17 (also referred to as gp100) (Ref. 115) have been detected in the sera of patients with vitiligo. Recently, the transcription factors SOX9 and SOX10 have been identified as melanocyte autoantigens related to vitiligo in patients with autoimmune polyglandular syndrome type 1 (Ref. 116). A summary of the antibody autoantigens implicated in the disorder is given in Table 4.

How could anti-melanocyte antibody reactivity arise and cause vitiligo?

The exact role of anti-melanocyte antibodies in the pathogenesis of vitiligo remains unresolved. Autoantibodies against pigment cells might result from a genetic predisposition to immune dysregulation at the T-cell level, as discussed earlier. Alternatively, crossreacting antigens expressed either on other target cells or on infecting microorganisms could elicit their production. Vitiligo autoantibodies could also result from an immune response to melanocyte antigens released following damage to pigment cells by other mechanisms, and these antibodies might then exacerbate the condition. The selective destruction of melanocytes might result from antibody reactivity directed to the antigens preferentially expressed on pigment cells (Ref. 111), or from an antibody response against antigens expressed on a variety of cell types (Ref. 107) that might selectively destroy melanocytes because they are intrinsically more sensitive to immune-mediated injury than, for

Table 4. Pigment cell antigens recognised by vitiligo autoantibodies (tab004hks)

Antigen	System of detection	Number of patients in study	Percentage with reactivity	Ref.
Tyrosinase	Immunoblotting of recombinant human tyrosinase	26	61	109
Tyrosinase	ELISA of mushroom tyrosinase	18	Not given	110
Tyrosinase	Radiobinding assay of recombinant human tyrosinase	46	11	111
TRP2	Radiobinding assay of recombinant human TRP2	53	5	114
TRP2	ELISA of recombinant human TRP2	30	67	113
TRP1	Radiobinding assay of recombinant human TRP1	53	5	112
Pmel17	Radiobinding assay of recombinant human Pmel17	53	5	115
40–45 kDa	Immunoprecipitation of human melanocytes	29	72	108
75 kDa	Immunoprecipitation of human melanocytes	29	76	108
90 kDa	Immunoprecipitation of human melanocytes	29	45	108
65 kDa	Immunoblotting of human melanocytes	18	44	146
35 kDa	Immunoprecipitation of human melanocytes	23	4	107
150 kDa	Immunoprecipitation of human melanocytes	23	4	107

Abbreviations: ELISA, enzyme-linked immunosorbent assay; TRP, tyrosinase-related protein.

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example, keratinocytes or fibroblasts (Ref. 117). It is also still possible that anti-melanocyte antibodies arise from an immune reaction to damaged pigment cells but play no part in vitiligo aetiology.

Other antibody reactivities

Circulating organ-specific autoantibodies, particularly to the thyroid, adrenal glands and gastric parietal cells, are commonly detected in the sera of vitiligo patients (Table 5) (Refs 30, 118, 119, 120). Anti-keratinocyte intracellular antibodies that correlate with disease extent and activity have also been detected in vitiligo patients (Ref. 121), and specific IgA reactivity against human melanoma cells in patients who have active vitiligo has been reported (Ref. 122). It has been demonstrated that benzene-derived chemicals including phenol and catechol can induce cutaneous depigmentation. Although the nature of their action has not been proven, high titres of antibodies against the benzene ring structure have been demonstrated in vitiligo patients (Ref. 123), suggesting that exposure to such compounds might play a part in the induction of aberrant immunological responses in individuals with chemically induced vitiligo (Ref. 123).

Melanoma-associated hypopigmentation

An interesting clinical facet of approximately 10% of patients with metastatic malignant melanoma, a cancer of the skin characterised by the uncontrolled growth of melanocytes, is the spontaneous development of vitiligo-like depigmentation (Ref. 124). In some cases, this phenomenon has been associated with an improved prognosis (Refs 125, 126), although other studies have reported no significant survival advantage for melanoma patients who develop hypopigmentary lesions (Ref. 127). In animal models of melanoma such as the Sinclair swine (a miniature pig prone to develop melanoma) (Ref. 128), melanoma progresses more slowly or even regresses in those animals in which vitiligo-like depigmentation develops in conjunction with the melanoma. Both cellular- and antibody-mediated immune responses to pigment cells apparently correlate with tumour regression and hypopigmentation in these animals (Refs 78, 129). Such observations have led to the postulation that the appearance of vitiligo-like hypopigmentation in some melanoma patients results from immune responses to pigment cell antigens that are shared by normal melanocytes and melanoma cells (Ref. 130). Indeed, autoantibody responses to pigment cell antigens have been observed in some

Table 5. The frequency of organ-specific autoantibodies in vitiligo patients (tab005hks)

Autoantibody reactivity	Number of patients in study	Percentage with antibody reactivity	Ref.
Gastric parietal cells	65	17	30
Gastric parietal cells	80	21	119
Gastric parietal cells	96	13.7	120
Gastric parietal cells	20	30	118
Thyroid cytoplasm	80	28	119
Thyroid microsomes	96	20	120
Thyroid microsomes	20	50	118
Thyroglobulin	80	9	119
Thyroglobulin	20	40	118
Adrenal gland	80	4	119
Pancreatic islet cells	96	7.2	120

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melanoma patients (Ref. 131). These include reactivities to tyrosinase, TRP1, TRP2 and Pmel17 (Ref. 132), as well as the 40–45 kDa, 75 kDa and 90 kDa antigens (Ref. 131) that are recognised by antibodies in vitiligo patients. CTLs that recognise melanocyte proteins tyrosinase (Ref. 133), TRP1 (Ref. 134), TRP2 (Ref. 135), Pmel17 (Ref. 136) and MelanA (Ref. 137) have also been repeatedly identified in patients with melanoma.

Specific studies concerning antibody reactivities in melanoma patients with associated hypopigmentation have documented responses to TRP2 (Ref. 113), melanoma cells (Refs 124, 138) and tyrosinase (Refs 138, 139). Whether or not such antibodies are responsible for initiating melanocyte destruction in these patients has not been determined. They might arise as a secondary immune response to melanocyte proteins following damage to pigment cells by other mechanisms. In addition, the exact role of T cells in the spontaneous development of melanoma-associated hypopigmentation has yet to be established.

Immunological approaches to melanoma treatment have also resulted in the development of vitiligo-like lesions in some patients. For example, the administration of IL-2 induced depigmentation in 20% of patients (Ref. 140). In addition, vaccination with melanocyte antigens, to initiate an anti-melanoma immune response, has resulted in the development of vitiligo-like lesions in melanoma patients (Ref. 113). The immune mechanisms involved in this phenomenon have been well studied in a mouse model (Refs 141, 142, 143). Both depigmentation and melanoma rejection was induced in C57BL/6 mice following immunisation with TRP1 cDNA (Refs 141, 142). High titres of anti-TRP1 antibodies were detected in the vaccinated mice, and $CD4^+$ T cells were an integral part of the processes of tumour cell destruction and hypopigmentation (Ref. 142). By contrast, immunisation of mice with TRP2 cDNA resulted in a response by $CD4^+$ T cells and $CD8^+$ CTLs but no antibody reaction, and again led to depigmentation and tumour rejection (Ref. 143). Melanoma patients immunised with a polyvalent melanoma cell vaccine have been shown to develop both depigmented lesions and an antibody response to TRP2 (Ref. 113), although T-cell reactivities were not examined in these individuals. Furthermore, the patients had a favourable survival outcome. A recent study reported the development of vitiligo in a melanoma patient receiving MelanA-specific $CD8^+$ T cells (Ref. 144). The depigmented lesions were infiltrated by the infused T cells, providing the first evidence that T-cell-mediated events can cause vitiligo in humans following specific immunotherapy. Overall, these studies suggest that immune responses to common antigens present on melanoma cells and normal melanocytes can occur after active, specific immunotherapy, which results in depigmentation and tumour rejection.

The above studies of the immune responses that cause depigmentation in melanoma might have some bearing on the pathogenesis of vitiligo. However, although melanoma-associated hypopigmentation (either spontaneously occurring or induced) and autoimmune vitiligo have a similar clinical appearance, and both can be associated with abnormal immune reactivities to pigment cell antigens, it has not yet been established if they have an identical aetiology. As some investigators have shown, different immune mechanisms can be responsible for depigmentation depending on the antigen involved (Refs 142, 143). Furthermore, studies that have tried to unravel the relationship between melanoma and the hypopigmentation with which it is sometimes associated have concentrated upon immune reactivities to melanogenic antigens (Refs 141, 142, 143). However, the role of such proteins in the pathogenesis of vitiligo remains controversial. For example, autoantibodies to tyrosinase, TRP1, TRP2 and Pmel17 have been reported to occur at low frequencies, or not at all, in vitiligo patients (Refs 111, 112, 114, 115, 145) and, so far, specific T-cell reactivities have only been identified to the melanocyte-specific proteins tyrosinase and MelanA (Ref. 85).

Clinical implications and applications

Research in the area of immunopathogenic mechanisms in vitiligo has several potential clinical implications and applications. Research into the abnormal immune responses that can occur in vitiligo patients might lead to the development of more-effective therapies for the condition, as well as a better understanding of the immunosuppressive treatments such as PUVA that are currently in use. The identification of melanocyte autoantigens recognised by either autoantibodies or autoreactive T cells in vitiligo patients might be of use in the diagnosis of the disorder. If aberrant immune reactions can be

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identified routinely, more-appropriate treatments could be applied to particular patients. The characterisation of melanocyte autoantigens that can elicit either a cellular or a humoral immune response to pigment cells in vitiligo could have implications for the development of peptide/gene-based vaccines for the treatment of melanoma.

Research in progress and outstanding research questions

Immunoregulatory genes

Research is being carried out to identify genes, including those with an immunoregulatory role, that might influence the development of vitiligo in some patients. Both case–control and family-based association studies are being undertaken.

Identification of autoantigens

New autoantigens that are recognised by autoantibodies and autoreactive T cells in vitiligo patients are currently being identified by using innovative approaches such as phage-display technology and HLA–peptide tetrameric complexes, respectively.

Nature of the immune response

Ongoing studies are attempting to establish whether the abnormal immune reactions to melanocytes that occur in some vitiligo patients are the primary cause of the disorder or whether they result from an immunological response to melanocyte antigens released from pigment cells following damage by other mechanisms. The exact role of anti-melanocyte autoantibodies and autoreactive T cells in vitiligo, and the reason for their appearance, has yet to be determined. The biggest question from the clinician's point of view is why a disease with an apparent immunological basis so very rarely shows clinical inflammation. This is very unusual for the skin, which readily exhibits inflammation in conditions such as eczema, psoriasis, and all inflammatory bullous disorders.

Clinical subsets of vitiligo

It is not known whether the different clinical subsets of vitiligo (e.g. generalised, segmental, focal) have different aetiologies – in particular, whether the vitiligo associated with autoimmune diseases has a different pathological mechanism from the vitiligo found in patients without any autoimmune disease. These are important questions as they might determine the most appropriate treatment for different patients.

Vitiligo and melanoma-associated hypopigmentation

The relationship between vitiligo and melanoma-associated hypopigmentation needs to be elucidated. Specifically, it is not known if the same immunological mechanism causes the cutaneous depigmentation observed in both these conditions. In this context, research into the immunopathomechanisms in vitiligo might play an important part in the development of effective therapies for melanoma.

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Further reading, resources and contacts

Reviews

The following recent review articles on vitiligo summarise the varied clinical presentations of the disease, the relationship between vitiligo and melanoma, theories of the aetiology of the disorder, and the different treatments currently available. Reviews concerning the melanocyte and melanogenesis are also included.

Boissy, R.E. and Nordlund, J.J. (1995) Vitiligo. In Cutaneous Medicine and Surgery (Arndt, K.A. et al., eds), pp. 1210-1218, W. B. Saunders Co, Philadelphia, PA, USA

Boissy, R.E. and Nordlund, J.J. (1995) Biology of melanocytes. In Cutaneous Medicine and Surgery (Arndt, K.A. et al., eds), pp. 1203-1209, W. B. Saunders Co, Philadelphia, PA, USA

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Hearing, V.J. (2000) The melanosome: the perfect model for cellular responses to the environment. Pigment Cell Res 13, 23-34, PubMed ID: 20494752

Kawakami, Y. et al. (2000) T cell immune responses against melanoma and melanocytes in cancer and autoimmunity. Pigment Cell Res 13, 163-169, PubMed ID: 20494774

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Russo, E. (1999) Harnessing the vitiligo effect. The onset of one disease may play a role in treating another. The Scientist 13, 1-4

Schallreuter, K.U. (1999) A review of recent advances on the regulation of pigmentation in the human epidermis. Cell Mol Biol 45, 943-949, PubMed ID: 20106814

Song, Y.H. (1997) Why tyrosinase for treatment of melanoma. Lancet 350, 82-83, PubMed ID: 97372901

Taieb, A. (2000) Intrinsic and extrinsic pathomechanisms in vitiligo. Pigment Cell Res 13, 41-47, PubMed ID: 20494754

Organisations

The organisations listed provide funds for research into establishing the cause of vitiligo and into finding a safe and effective treatment. Some also offer support to vitiligo sufferers and their families, as well as providing information about the disorder.

The Vitiligo Society

http://www.vitiligosociety.org.uk

The National Vitiligo Foundation

http://www.nvfi.org

The American Vitiligo Research Foundation

http://www.vitiligosearch.org

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The British Skin Foundation

19 Fitzroy Square, London, W1T 6EH, UK.
Tel: +44 020 7383 0266; Fax: +44 020 7388 5263

Professional societies

The following professional societies have the subject of vitiligo within their remit, and current research concerning the aetiology and treatment of the disease is presented at their annual meetings.

British Society for Investigative Dermatology

Department of Dermatology, University of Newcastle, Newcastle-Upon-Tyne, NE2 4HH, UK.
Tel: +44 0191 222 5840; Fax: +44 0191 222 7094

European Society for Dermatological Research

http://dermatology.azn.nl/esdr/

Society for Investigative Dermatology

http://www.sidnet.org

American Academy of Dermatology

http://www.aad.org

European Society for Pigment Cell Research

http://www.ulb.ac.be/medecine/loce/espcr.htm

PanAmerican Society for Pigment Cell Research

http://www.cbc.umn.edu/paspcr

International Federation of Pigment Cell Societies

http://www.cbc.umn.edu/ifpcs

Additional internet sites

The following websites provide information about vitiligo as well as the opportunity to contact scientists and clinicians studying the disease and patients who suffer from the disorder.

Vitiligo Switchboard

http://web.onramp.ca/cadd/vitiligo.htm

Vitiligo Support.com

http://www.vitiligosupport.com

Yahoo Vitiligo Support Group

http://clubs.yahoo.com/clubs/vitiligosupportgroup

Vitiligo Support and Information Group

http://www.lsoft.com/SCRIPTS/WL.EXE?SL1=VITILIGO&H=MAELSTROM.STJOHNS.EDU

Handbook of Dermatology and Venereology: Vitiligo

http://www.hkmj.org.hk/skin/vitiligo.htm

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Features associated with this article

Figures

Figure 1. Loss of melanocytes in epidermis affected by vitiligo (fig001hks).
Figure 2. Bilateral symmetrical vitiligo on the dorsal aspects of the hands (fig002hks).
Figure 3. Summary of the possible cellular and humoral immune mechanisms of vitiligo (fig003hks).

Tables

Table 1. Therapies for vitiligo (tab001hks).
Table 2. Association of vitiligo with autoimmune disorders (tab002hks).
Table 3. Major histocompatibility complex antigen associations with vitiligo (tab003hks).
Table 4. Pigment cell antigens recognised by vitiligo autoantibodies (tab004hks).
Table 5. The frequency of organ-specific autoantibodies in vitiligo patients (tab005hks).

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