



HANDBOOK OF VITILIGO

BASIC SCIENCE AND CLINICAL MANAGEMENT

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15/09/2015 16:59

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2 Immunopathogenesis

John E. Harris

Introduction

The pathogenesis of vitiligo has been controversial for the past few decades. Hypotheses offered to explain clinical observations included autoimmune, melanocyte-intrinsic, neurologic, and genetic mechanisms. In a recent review, differing views were described as 'hotly disputed for as long as one remembers . . . a magnet for endless speculation' (Schallreuter et al. 2008). A neurologic mechanism for vitiligo pathogenesis is probably the least well supported, based largely on the unilateral nature of the segmental subtype of vitiligo and the appearance of an increased level of catecholamines in the urine of patients with vitiligo compared to controls. Catecholamines are a product of tyrosine metabolism, and although nerves are common sources of these chemicals (e.g. epinephrine, norepinephrine, and dopamine), melanocytes are also possible sources, as melanogenesis depends on tyrosine metabolism as well. Patients with melanoma metastases have been reported to excrete increased levels of catecholamines. Cutaneous innervation is certainly unilateral – evident by reactivation of varicella zoster (shingles) that follows dermatomes. However, segmental vitiligo rarely follows a single dermatome and often crosses multiple dermatomes. For this reason, using the term 'dermatomal vitiligo' or even 'quasi-dermatomal vitiligo' is not an accurate description of this subtype, suggesting a neurologic pathogenesis that is not supported. Thus, the term 'dermatomal vitiligo' should no longer be used, and this chapter will not discuss neurologic mechanisms further. Instead, it will focus on autoimmune, melanocyte-intrinsic, and genetic mechanisms – hypotheses that are well-supported in the literature and not mutually exclusive. The pathogenesis of the segmental subtype of vitiligo is not fully clear; however, its possible etiology will be discussed at the end of the chapter.

In 1940, the clustering of vitiligo cases within families was reported, supporting a genetic component to pathogenesis. As early as the 1960s, clinicians recognized an association between vitiligo and other diseases believed to have an autoimmune pathogenesis. Those with vitiligo and their close relatives appeared to have an increased risk of type 1 diabetes, thyroiditis, and pernicious anemia. In the early 1980s, patients with vitiligo were found to possess elevated levels of melanocyte-specific autoantibodies, which could damage melanocytes both in vitro and in vivo, supporting an autoimmune pathogenesis of vitiligo. However, antibodies do not necessarily correlate with disease activity, and distinct patches of skin are involved in vitiligo despite the systemic presence of antibodies in serum, suggesting that antibodies were not

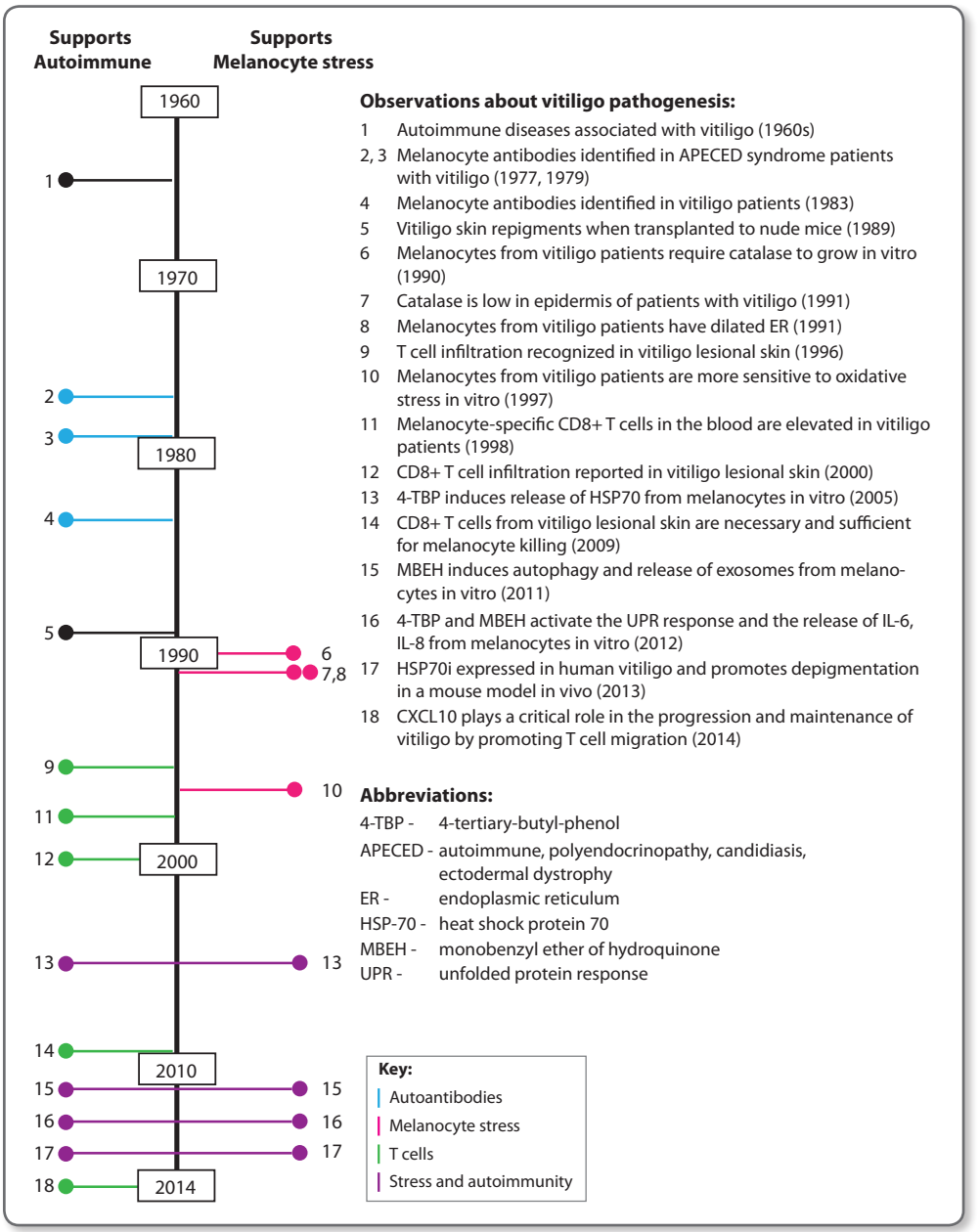

Figure 2.1 Timeline of selected discoveries addressing the pathogenesis of vitiligo. Early reports revealed that vitiligo was associated with autoimmune diseases and that patients had elevated levels of autoantibodies against melanocytes, supporting an immune contribution. Later studies revealed the presence of intrinsic defects in melanocytes, manifest as elevated levels of cellular stress, suggesting that melanocytes were not simply innocent targets of the immune system. T cells were then strongly implicated as key immune effectors responsible for melanocyte destruction. Finally, multiple studies connected melanocyte stress and autoimmunity together, revealing a unified theory that incorporated contributions from both melanocytes and the immune cells in the pathogenesis of vitiligo.

the entire answer. Thus, alternative theories were sought, beginning an interesting sojourn to identify the true pathogenesis of vitiligo. A timeline summarizing key observations concerning the pathogenesis of vitiligo discussed in this chapter is provided in **Figure 2.1**.

Melanocyte-intrinsic pathogenesis: cellular stress

In the late 1980s and early 1990s, multiple groups observed that in contrast to melanocytes from healthy patients, melanocytes isolated from unaffected skin of patients with vitiligo were difficult to culture in vitro, exhibiting a slow replication rate (Puri et al. 1987). Culture conditions had to be modified to improve growth, including the addition of growth factors or catalase to the culture media. Electron microscopy of cellular substructure revealed that the endoplasmic reticulum in melanocytes from patients with vitiligo was dilated compared to healthy controls, implying elevated cellular stress. This hypothesis was supported by reports of elevated levels of H_2O_2 and oxidative by-products in the epidermis of patients with vitiligo compared to controls – a general measure of the level of reactive oxygen species (ROS) (Schallreuter et al. 1999). Consistent with these observations, the enzyme catalase, which reduces H_2O_2 to O_2 and H_2O, thereby 'detoxifying' the molecule and relieving oxidative stress, was found to be decreased in lesional skin (Schallreuter et al. 1991), which may be either a cause or an effect of increased H_2O_2. Based on these observations, treatment of disease with topical exogenous catalase has been attempted, showing variable results (Gawkrodger 2009).

In support of a stress mechanism of vitiligo, exposure of cultured melanocytes to induced stress in vitro (e.g. ultraviolet B, heat shock, and peroxide) led to the death of melanocytes from patients with vitiligo but not from healthy patients (Maresca et al. 1997). Despite the fact that toxicity leading to death was only observed in vitro without direct correlation in vivo, and was the result of supraphysiologic stimuli, these observations led to the theory that vitiligo pathogenesis was entirely due to intrinsic melanocyte defects, and that any immune component was secondary, to 'mop up' cellular debris after melanocyte apoptosis.

The production of melanin is hazardous work. First, producing large amounts of protein increases the risk of generating misfolded proteins, which activates the unfolded protein response (UPR) – a cellular stress response. Second, the increased energy requirements of protein production lead to the creation of ROS from energy metabolism in mitochondria. Third, the position of melanocytes in the epidermis exposes them to ultraviolet light, which generates intracellular ROS, hydrogen peroxide, and superoxide anions. Finally, and most specific for melanocytes, the chemical modifications made by tyrosine hydroxylase and phenylalanine hydroxylase required to convert the amino acid tyrosine into melanin liberates hydrogen peroxide, a precursor to ROS (Meyskens et al. 2001), which can directly activate the stress response.

Therefore, the melanocyte-intrinsic theory of vitiligo pathogenesis seemed reasonable, resulting in a healthy skepticism for any role of autoimmunity in the disease. However, an important observation by Gilhar and colleagues strongly suggested that neither melanocyte-intrinsic defects nor even the microenvironment of the skin were sufficient for disease. Transplantation of lesional, depigmented skin from patients with vitiligo to nude mice resulted in rapid repigmentation of the skin graft, revealing that additional, systemic factors outside of the skin were necessary, at least for the maintenance of depigmentation in vitiligo (Gilhar et al. 1989).

Autoimmune pathogenesis

T-cell cytotoxicity

Most skin biopsies in patients with vitiligo reveal little to no immune infiltrate; however, in the mid-1990s, clinical studies began to report a patchy T-cell infiltrate in the superficial dermis that localized to the dermal–epidermal junction, where melanocytes reside. In particular, T cells were able to infiltrate the epidermis and were found in direct apposition to dying melanocytes and melanocyte fragments. Most of these cells were CD8+/perforin+/granzyme+, consistent with a cytotoxic phenotype (Van den Wijngaard et al. 2000). Initial studies examined lesional skin of patients with inflammatory vitiligo, which is an uncommon and highly inflammatory form of the disease; these observations were later extended to typical, noninflammatory forms as well.

Another group further implicated cytotoxic T cells in vitiligo by identifying melanocyte-reactive CD8+ T cells in the blood of patients. To do this, class I HLA tetramers were loaded with Mart-1 (MelanA) peptide, a melanocyte-specific antigen, and labeled with a fluorescent probe. In this scenario, these reagents then interact with antigen-specific CD8+ T cells through their T-cell receptor, much as a melanocyte would. Interacting cells are therefore made fluorescent, identifiable through flow cytometry (**Figure 2.2**). Using this approach, labeled cells were found to be more prevalent in patients with vitiligo compared to healthy controls, and tetramer-positive (melanocyte-specific) cells were specifically able to kill melanocytes in vitro, whereas tetramer-negative cells did not (Ogg et al. 1998).

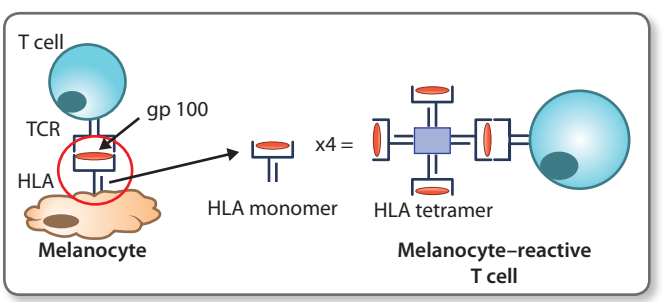

Figure 2.2 HLA tetramers label melanocyte-specific autoreactive T cells in the blood of patients with vitiligo. HLA molecules expressed on all nucleated cells present peptide antigen to T cells and can be used to label autoreactive T cells using flow cytometry.

These findings were later confirmed by identifying elevated levels of melanocyte-reactive CD8+ T cells in both blood and lesional skin from patients with vitiligo compared to controls, using tetramers loaded with additional melanocyte-specific peptides, including gp100 and tyrosinase. However, the definitive observation implicating melanocyte-specific, cytotoxic T cells in the pathogenesis of vitiligo was reported by Van den Boorn and coworkers. In this study, T cells were isolated from perilesional vitiligo skin and cocultured with unaffected, normally pigmented skin explants from the same patient. Total T cells and CD8+ T cells infiltrated the normal skin explants, migrated to the epidermis, and induced apoptosis in melanocytes, whereas CD8+-depleted T cells did not (Van den Boorn et al. 2009). This demonstrated that CD8+ T cells were necessary and sufficient for the destruction of melanocytes in vitiligo. Although CD4+ 'helper' T cells are often required to enhance the effector function of CD8+ T cells in response to infection, a clear role for them in vitiligo has not yet been clearly defined, despite their consistent presence in the superficial dermis in lesional biopsies of the skin.

Cytokines/chemokines

T cells execute effector functions largely through the secretion of cytokines and chemokines that have autocrine and paracrine effects both locally and over large distances. Certain cytokine/chemokine families have emerged that mediate specific types of immune responses, providing tools for the immune system – each specific to a particular condition. This is much like the way a country's military might be divided into army, navy, air force, and marines, with each being used for a specific purpose. These immune responses may be grouped according to the types of cytokines produced by CD4+ T cells, including T_H1 (IL-12, IFN-γ), T_H2 (IL-4, IL-5, IL-13), and T_H17 (IL-23, IL-17, IL-22) subtypes. Numerous studies have been performed to measure the levels of cytokines in the blood of patients with vitiligo compared to controls, showing variable results. Many reveal small increases in cytokine levels of IFN-γ, TNF-α, IL-4, IL-17, IL-6, and others; however, these cytokines often play opposing roles in immunity, the studies did not always agree with one another, and the blood does not necessarily represent what is occurring within the skin.

Studies conducted by the author and others sought to determine which cytokines and chemokines were expressed within the skin during T-cell–mediated destruction of melanocytes in vitiligo. These observations revealed that IFN-γ was the primary cytokine expressed in active human lesional skin, as well as in a mouse model of vitiligo with very close similarities to human vitiligo. Functional studies revealed that IFN-γ was required for vitiligo in the mouse, as blocking the cytokine inhibited the development of depigmentation (Harris et al. 2012). In addition, the IFN-γ–induced chemokine, CXCL10, is highly expressed both in human lesional skin and in mouse skin, and its receptor, CXCR3, is expressed on melanocyte-specific CD8+ T cells in

the blood and skin of patients. Chemokines such as CXCL10 are known to act as homing signals to recruit T cells into peripheral tissues like the skin, as well as promote the effector activity of T cells once they arrive. Further studies revealed that without CXCR3, T cells were unable to migrate to the skin and cause vitiligo, and if CXCL10 were eliminated genetically or neutralized with an antibody, depigmentation was abrogated. Interestingly, these experiments also suggested that CXCL9 might specifically promote T-cell migration into the dermis from the circulation, whereas CXCL10 helps to localize the T cells to the epidermis where melanocytes reside (**Figure 2.3**). Importantly, even mice with widespread depigmentation experienced reversal of disease after treatment with CXCL10 antibody, revealing that this cytokine/chemokine pathway was required for both the progression and maintenance of disease (Rashighi et al. 2014). Therefore, targeting this pathway might provide a new treatment strategy for patients with vitiligo. This could be accomplished with antibodies against CXCL10 or CXCR3, as well as small molecule inhibitors of CXCR3, which have been developed by several pharmaceutical companies.

T-regulatory cells

T-regulatory cells, or Tregs, are important cells in the immune system, responsible for suppressing inappropriate immune responses against self-tissues. Therefore, many have hypothesized that they play an important role in preventing vitiligo, and that defects in their number or function might be an important mechanism by which patients with vitiligo lose self-tolerance and develop disease. Indeed, mouse studies have supported this concept, as eliminating Tregs worsens depigmentation, whereas increasing Tregs abrogates depigmentation in these models. The identification of BACH2 as a risk gene for vitiligo may indicate a role for Tregs in human vitiligo, as BACH2 is

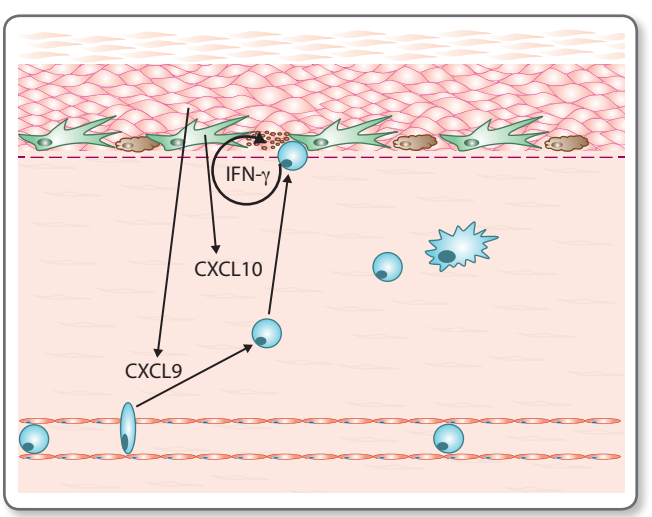

Figure 2.3 Role of CXCL9 and CXCL10 in localizing autoreactive T cells to find melanocytes in the epidermis. CXCL9 may promote T-cell migration into the dermis from the circulation, whereas CXCL10 may attract T cells to the epidermis where melanocytes reside. Once correctly localized within the skin, T cells recognize melanocytes, produce IFN-γ, and destroy them.

a key transcription factor that limits T-effector differentiation and promotes the generation of Tregs (Roychoudhuri et al. 2013, Spritz 2013). However, functional human studies in vitiligo have been less clear: one group reported decreased numbers of Tregs in the blood of patients with vitiligo compared to controls; increased numbers were reported in another group; no difference in number but a decrease in functionality was reported in another group; and no difference in number or functionality but a decreased ability to home to the skin was reported in yet another group. It is likely that patients have distinct abnormalities that predispose their disease and that Tregs do play a role. However, current methods used to study them in humans are not sufficient to generate a consensus for their role, and further studies with more precise measures of their functionality will be required.

Chemical leukoderma: the convergence of two theories

The data presented earlier combined with the historical observations of coinheritance of vitiligo with other autoimmune diseases, the production of melanocyte-specific autoantibodies, the fact that 'adoptive transfer' of vitiligo has been observed in patients receiving bone marrow/stem cell transplants, and the immunosuppressive nature of all effective therapies for vitiligo (topical steroids, topical calcineurin inhibitors, and narrowband ultraviolet B light) clearly define a critical role for autoimmunity in vitiligo pathogenesis. However, this understanding had not yet been reconciled with the well-documented intrinsic defects in melanocytes described previously. Le Poole and colleagues first suggested that these conflicting observations might be reconciled into a 'convergence theory' requiring multiple steps in vitiligo pathogenesis (Le Poole et al. 1993). Experimental evidence for this theory would come almost 20 years after its inception, in the form of chemically induced vitiligo, or chemical leukoderma.

For years, clinicians have recognized the phenomenon of depigmentation following skin contact with certain chemicals, often referred to as 'chemical leukoderma.' First recognized in 1939 by Oliver and coworkers and labeled as 'occupational vitiligo,' chemical-induced depigmentation was described in a small subset of workers who wore acid-cured rubber gloves in a leather factory. Monobenzyl ether of hydroquinone, or monobenzone, was identified as the causative agent (Oliver et al. 1939). Since then, a series of reports have confirmed this observation, adding to the list of chemicals that induce depigmentation. Offending agents include phenolic and catecholic chemicals found in dyes (including hair dyes), resins/adhesives, leather footwear and wallets, and others. The common feature of these agents is that they possess a benzene ring, and most often a phenol group, a chemical structure similar to tyrosine, which is the substrate for the production of melanin. Although depigmentation begins localized to the site of exposure, it may also (>26% of the time) spread to distant sites as well (Ghosh & Mukhopadhyay 2009).

Monobenzone is used therapeutically to complete the depigmentation of patients with severe vitiligo, providing an even skin tone. Depigmentation therapy is accomplished through topical treatment with 20% monobenzone cream, applied twice daily to areas of remaining pigment. Over a period of 4–12 months, patients gradually lose this pigment and become white all over, or 'bleached,' and most are pleased with the results. Hairs are unaffected by the treatment, and repigmentation of the skin from the hair may occur at any time following treatment. Retreatment with monobenzone typically is effective. The mechanism of depigmentation following treatment with monobenzone, or any agent inducing chemical leukoderma, has long been a mystery. As seen in chemical leukoderma, depigmentation is not restricted to the treated area but can depigment areas remote from contact with the agent.

Recent studies have revealed potential mechanisms of chemical leukoderma, providing a connection between the two seemingly opposing theories: autoimmunity versus cellular stress. In 2005, Kroll and colleagues found that 4-tertiary butyl phenol (4-TBP), a mediator of chemical leukoderma that also initiates cellular stress in melanocytes. In turn, this increased the production of a heat shock protein 70 (HSP70i) in cultured melanocytes. HSP70i was released into the cell culture media and induced the activation of dendritic cells cocultured with melanocytes to become cytotoxic and kill them in vitro (Kroll et al. 2005). In 2011, van den Boorn and coworkers connected melanocyte stress to T-cell–mediated (antigen-specific) autoimmunity when they described the effects of monobenzone on melanocytes. Monobenzone has a chemical structure similar to tyrosine and is taken up by tyrosinase, which attempts to oxidize the chemical to produce melanin. However, monobenzone becomes covalently bound to the enzyme, which results in production of ROS, autophagy, and the release of melanocyte antigen-laden exosomes into the surrounding media. Cocultured dendritic cells take up the exosomes, become mature antigen presenting cells, and activate melanocyte-specific CD8+ T cells, therefore initiating an autoimmune response (Van den Boorn et al. 2011). Finally, Toosi et al. revealed that 4-TBP induces the UPR in melanocytes, which results in production of inflammation-inducing cytokines IL-6 and IL-8 (Toosi et al. 2012). Although all of these observations were made using a chemical inducer of oxidative stress in vitro, they provide a connection between the level of oxidative stress in the melanocyte and the production of proinflammatory mediators with strong potential to initiate or exacerbate an autoimmune response (**Figure 2.4**).

Innate immunity

Since the observation that HSP70i was released from melanocytes following exposure to 4-TBP, its role in activating dendritic cells and contributing to vitiligo pathogenesis has been further studied in patients and in a mouse model of vitiligo. HSP70i appears to be

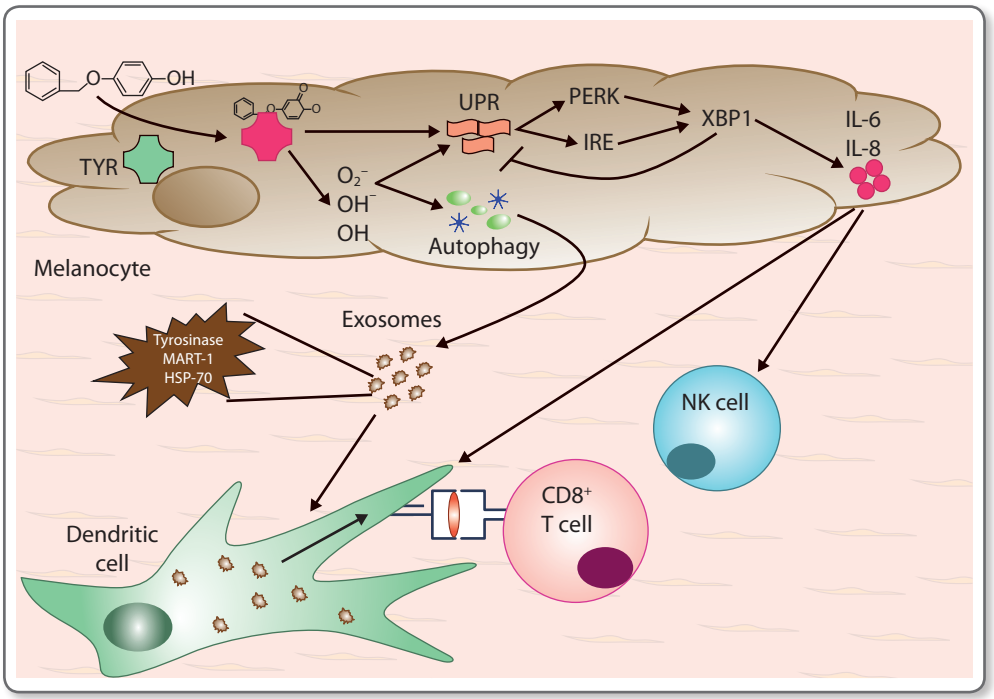

Figure 2.4 Summary of the melanocyte stress–immune interface. Chemical melanocyte stressors (monobenzone is shown) resemble tyrosine and interact with tyrosinase, which activates two stress pathways: (1) the unfolded protein response (UPR) and (2) reactive oxygen species (ROS). The UPR induces expression of XBP1, which negatively regulates the stress response, but also induces the proinflammatory cytokines IL-6 and IL-8. ROS also activate the UPR and initiate autophagy of melanosomes, resulting in the release of proinflammatory HSP70i and exosomes. These proinflammatory mediators encourage cellular immunity through dendritic cell and cytotoxic T-cell activation, which ultimately leads to melanocyte destruction.

expressed at elevated levels in perilesional skin of patients with vitiligo, and introducing the protein during induction of vitiligo in mice worsens the disease. In fact, a mutated form of HSP70i was shown to dampen the severity of vitiligo in mice and has been offered as a new treatment strategy (Mosenson et al. 2013). Together with the fact that melanocyte stress-induced secretion of HSP70i and exosomes activate dendritic cells, these observations suggest that dendritic cells make important contributions to vitiligo pathogenesis. Other groups have described increased numbers of dendritic populations in perilesional vitiligo skin, supporting this hypothesis.

Dendritic cells are key players in the initiation of inflammation, as they take up abnormal proteins and present them as antigens to activate T cells to differentiate, produce chemokines, and become cytotoxic effectors. In addition to taking up and presenting antigens, they express a variety of innate pattern recognition receptors (PRRs), which detect 'danger signals' that are present during infection with pathogens (i.e. pathogen-associated molecular patterns, or PAMPs)

and also during sterile-induced destruction of tissue (i.e. damage-associated molecular patterns, or DAMPs). PRR ligation of these danger signals results in maturation of the dendritic cells and the production of proinflammatory cytokines to initiate immune responses. Therefore, HSP70i, exosomes, and other signals released by melanocytes when under stress may act as danger signals that initiate inflammation in vitiligo (Richmond et al. 2013).

In addition to an infiltration of dendritic cells in active vitiligo lesions, others have reported that even normal skin in patients with vitiligo contains increased numbers of innate immune cells, particularly natural killer cells (Yu et al. 2012). Natural killer cells are capable of recognizing cellular stress and producing IFN-γ. Therefore, they may connect innate immunity to adaptive immunity, considering the importance of IFN-γ–induced CXCL10 in recruiting autoreactive T cells to lesional skin in vitiligo. The signals required for this influx of cells in normal-appearing skin in patients with vitiligo is unknown; however, inflammatory signals arising from DAMP-induced PRR activation could play a role. These observations are summarized in **Figure 2.5**.

Genetic evidence

Although entirely focused on chemical-induced melanocyte stress and death in vitro, these studies provide a plausible connection between inherent melanocyte stress observed in patients with vitiligo and the clear role for autoreactive CD8+ T cells in disease pathogenesis. Genome-wide linkage and association studies have provided additional evidence for the stress and autoimmunity hypothesis. The earliest genetic associations were with the HLA-A haplotypes, supporting an autoimmune pathogenesis. The first non-HLA gene found to confer risk for vitiligo was NLR family,

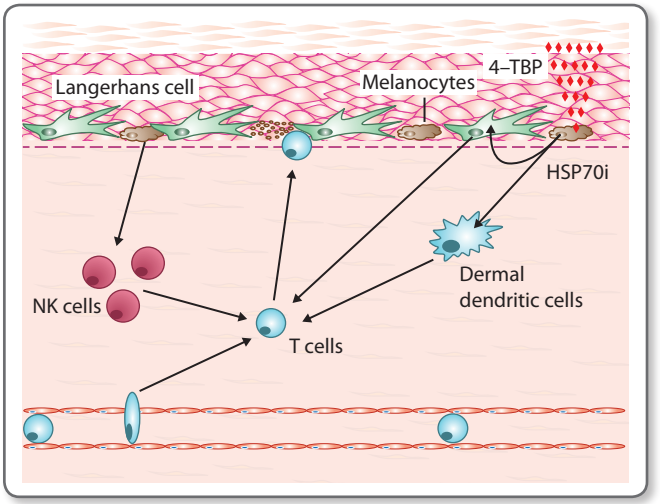

Figure 2.5 Innate immunity in vitiligo. Stressed melanocytes secrete HSP70i, which activates dendritic cells to become proinflammatory. Natural killer (NK) cells infiltrate even normal skin of patients with vitiligo. Both may contribute to vitiligo by promoting the recruitment of autoreactive T cells, although the signals that mediate this process are unknown.

pyrin domain containing 1 (NLRP1), also called NALP1. NLRP1 is a critical component of the inflammasome, a major signaling pathway in the innate immune response that leads to the production of IL-1β, confirming a causative role of the immune system in vitiligo (Jin et al. 2007). Functional genomic studies revealed that the vitiligo risk allele for NLRP1 results in increased production of IL-1β when compared to the protective allele, under both constitutive and stimulated conditions (Levandowski et al. 2013).

Further studies revealed a large number of additional genes, most of which play a role in immune responses (PTPN22, TSLP, HLA class I/II/III, CCR6, IL2RA, UBASH3A, and FOXP3), including specifically cytotoxic T-cell responses (GZMB), supporting earlier histologic and in vitro mechanistic data. Importantly, two additional genes include tyrosinase, the enzyme responsible for melanin production, and X-box binding protein 1 (XBP1), which is a member of the UPR that protects the cell from stress-induced apoptosis but can also promote IL-6, IL-8, and class II HLA expression (important for antigen presentation to CD4+ T cells) (Spritz 2013).

The role of tyrosinase may be related to its role as an autoantigen, and therefore recognition of melanocytes by the autoimmune T-cell response. However, as a direct target of ROS, tyrosinase variants may also play a role by participating in the stress response, such as susceptibility to chemicals, or through both mechanisms. Interestingly, the allele conferring susceptibility to vitiligo is protective for melanoma and vice versa. In addition to a proinflammatory role in vitiligo, XBP1 may also participate in the stress response, as changes in expression or activity of the protein could increase stress levels of the melanocyte, indirectly leading to autoimmunity. Consistent with this hypothesis, studies in inflammatory bowel disease have identified two hypomorphic variants of XBP1 that contribute to a proinflammatory state of the intestine as a result of increased cellular stress (Kaser et al. 2008). To date, only a hypermorphic variant has been described in vitiligo, which may induce an exaggerated inflammatory response to cellular stress. It is possible that either an increased or decreased expression/function of XBP1 will promote susceptibility to vitiligo. Further studies will be required to determine the exact role that genome-wide association studies play in disease pathogenesis.

Segmental vitiligo: a reflection of the immune cell–target cell interface?

Segmental vitiligo is a disease variant presenting with focal, unilateral involvement that rarely spreads beyond the initial site of depigmentation, in contrast to the typical symmetric distribution of disease (**Figure 2.6a**). It accounts for approximately 5% of all patients

with vitiligo and 19% of those who develop vitiligo in childhood. Its unilateral presentation has prompted much curiosity and discussion about its etiology, and it frequently is misclassified as 'dermatomal' despite the fact that depigmentation rarely, if ever, follows a single dermatome (Van Geel et al. 2012a). This misclassification has led to hypotheses that the pathogenesis of the segmental variant, and potentially all vitiligo, is related to sensory innervation of the skin. In addition, this unilateral presentation has been used as an argument against an autoimmune pathogenesis of vitiligo, as there are few known examples of unilateral autoimmunity. However, the skin is a unique organ in which diseases can be directly observed, and therefore

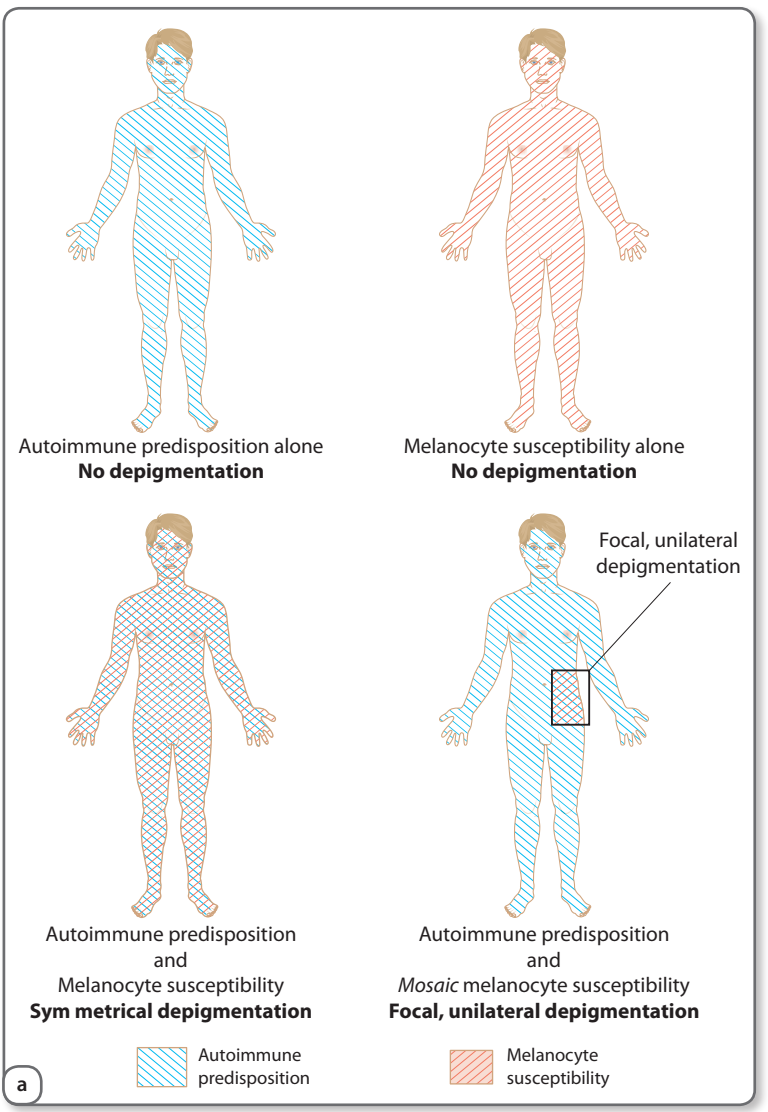

Figure 2.6a Segmental vitiligo. Hypothesis of universal autoimmune predisposition with overlapping focal, unilateral susceptibility of melanocytes. Autoimmune predisposition is universal, as T-cell migration is not regionally limited. Melanocyte susceptibility inherited through the germline is universal, as it is present in all cells. Either autoimmune predisposition or melanocyte susceptibility alone may be insufficient for depigmentation in vitiligo. When autoimmune predisposition and universal melanocyte susceptibility are both present, symmetrical depigmentation results, which is characteristic of typical vitiligo. A somatic mutation occurring in a melanocyte will be present unilaterally, in the 'field' of skin populated by the daughter cells of that cell during embryogenesis.

HANDBOOK OF VITILIGO

BASIC SCIENCE AND CLINICAL MANAGEMENT

Over the years there have been few truly effective treatments for vitiligo, but recent breakthroughs in the medical, phototherapeutic and surgical management of this disfiguring disease have brought new treatment options to clinicians and their patients.

Handbook of Vitiligo: Basic Science and Clinical Management discusses the full range of treatments available to physicians, from pharmacologic therapies to phototherapy and surgical procedures including tissue grafts and melanocyte transplants. The book also covers relevant basic science, the management of childhood vitiligo, and the role and importance of support groups for patients living with this challenging condition.

With contributions from a global team of experts, *Handbook of Vitiligo: Basic Science and Clinical Management* offers a concise, practical guide to help dermatologists, dermatologic surgeons and other healthcare providers devise the most effective treatment plans for their patients.

- Summarises latest best practice in both established medical therapies and emerging medical, surgical and phototherapeutic techniques
- Includes discussion of the complementary and alternative therapies commonly used by patients with vitiligo
- Provides practical guidance for assessing the impact of vitiligo on quality of life and advice on support groups for patients

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