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Chapter 7

Vitiligo – A Complex Autoimmune Skin Depigmenting Disease

Mitesh Dwivedi, Naresh C. Laddha,
Anthony P. Weetman, Rasheedunnisa Begum and
Helen Kemp

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1. Introduction

Vitiligo is an acquired, non-contagious disease in which progressive, patchy loss of pigmentation from the skin, overlying hair and oral mucosa results from the loss of melanocytes from the involved areas [1]. Clinically, two large subsets of vitiligo are distinguished namely focal or segmental vitiligo and non-segmental or generalised vitiligo [2]. Focal vitiligo presents with a limited number of small lesions while segmental vitiligo is typified by an asymmetric distribution involving segments of the skin surface, sometimes in a dermatomal fashion, by depigmented macules. Non-segmental vitiligo corresponds to all generalised, usually symmetrical, forms including acrofacial vitiligo. The course of the disease is unpredictable but is often episodically progressive with phases of stabilised depigmentation. Extending vitiligo with enlarging macules or the development of new lesions is classified as the active form of the disease [3].

Although vitiligo might be viewed as minor disorder, skin depigmentation can cause psychological stress in patients with respect to self-esteem and social interactions. This is particularly true for individuals with deeply pigmented skin [4], and for women who in some cultures face social and marital stigma [5]. The prevalence of vitiligo has been reported to be 0.5 to 1% of the world population [6,7]. In India, the prevalence varies from 0.5 to 2.5 % [8], although the states of Gujarat and Rajasthan have a prevalence of 8.8% [9]. Vitiligo affects all with no predilection for gender or race. The disease usually starts in childhood or young adulthood: the clinical manifestation begins before 20 years of age in 50% of cases, while in 25% of cases the onset is before the age of 14 years [10].

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Many factors have been implicated in the aetiology and pathogenesis of the vitiligo including infections [11], stress [12], neural abnormalities [13], defective melanocyte adhesion [14], and genetic susceptibility (Figure 1) [15]. The biochemical hypothesis argues that melanocyte destruction is due to the accumulation of toxic metabolites from melanogenesis, the breakdown of free-radical defence and an excess of hydrogen peroxide [16-18]. In addition, many studies have indicated a role for both cellular [19] and humoral [20] immunity in the pathogenesis of vitiligo. This chapter will focus on the available evidence which supports the involvement of autoimmunity in the aetiology and pathogenesis of vitiligo.

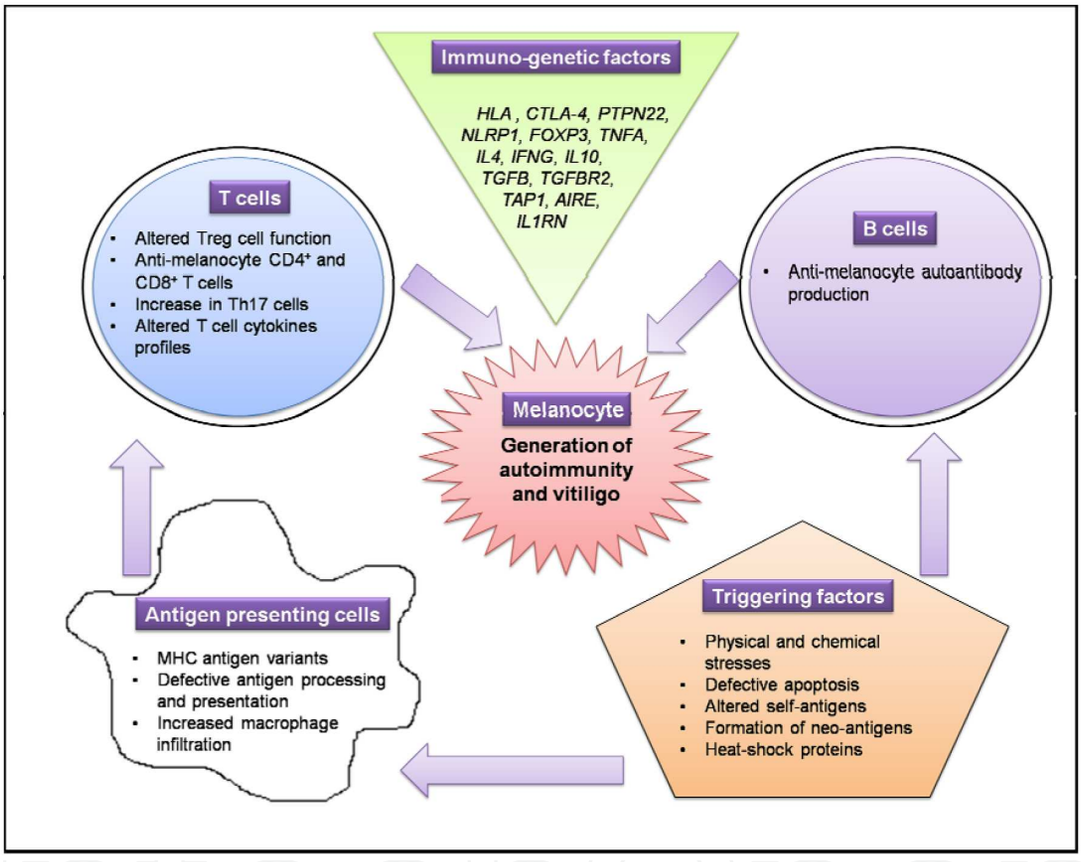


Figure 1. The generation of autoimmune responses against melanocytes in vitiligo. Depigmentation in vitiligo results from a hyperactive response of the immune system against melanocytes. A complex interaction of immune cells and immuno-genetic factors is the most likely aetiology. In particular, defects of T cell subsets as well as altered melanocyte antigens may give rise to increased autoreactive $CD8^+$and $CD4^+$T cells and the generation of anti-melanocyte autoantibodies. The triggering factors involved in generation of autoimmunity in vitiligo patients are still not clearly defined, although physical trauma and melanocyte oxidative stress have been implicated.

2. Association with autoimmune diseases

Vitiligo is frequently associated with other autoimmune disorders, particularly autoimmune thyroid disease [21]. Patients with vitiligo are also more likely to suffer from autoimmune

conditions than those in the general population [22]. For example, a survey of more than 2,600 unselected Caucasian vitiligo patients indicated elevated frequencies of autoimmune thyroid disease, Addison's disease, systemic lupus erythematosus and pernicious anaemia, and, indeed, approximately 30% of patients were affected by at least one other autoimmune disease [23]. Furthermore, the same autoimmune diseases were found at an increased prevalence in the first-degree relatives of vitiligo patients [23] and in multiplex vitiligo families [24]. Such findings indicate that vitiligo can be part of a specific group of autoimmune diseases to which individuals can be genetically predisposed, and are also evidence for its autoimmune pathogenesis.

3. Immuno-regulatory genes

The involvement of immune-regulatory genes with vitiligo development has been extensively documented [15]. For example, the association of certain major histocompatibility complex (MHC) alleles with vitiligo has suggested an important link between the aetiology of the disease and aberrant presentation of self-antigens to the immune system. Most recently, alleles of human leukocyte antigen (HLA) genes *HLA-A*33:01*, *HLA-B*44:03*, and *HLA-DRB1*07:01* have been reported to be significantly more prevalent in Indian vitiligo patients as compared with healthy controls [25]. In the European-derived white population, vitiligo shows primary association with *HLA-A* in the class I region [26], specifically *HLA-A*02:01* [27], and in the class II region upstream of *HLA-DRA* and located between *HLA-DRB1* and *HLA-DQA1*. Furthermore, studies of Chinese have shown MHC associations in the class I region, between *HLA-B* and *HLA-C* [28] and in the class III region [29].

Other immune-regulatory genes that contain single nucleotide polymorphisms associated with vitiligo susceptibility include *PTPN22* (lymphoid-specific protein tyrosine phosphatase, non-receptor type 22), *IL2RA* (interleukin-2 receptor alpha chain), *UBASH3A* (ubiquitin-associated and SH3 domain–containing A protein), and *C1QTNF6* (C1q and tumour necrosis factor–related protein) [26].

4. Immunological features of melanocytes

Several studies have shown abnormal expression of MHC class II antigen HLA-DR and increased expression of intercellular adhesion molecule-1 (ICAM-1) by perilesional melanocytes in vitiligo compared with melanocytes from normal skin [30-32]. These molecules have important roles in antigen presentation and in the activation of T helper cells, so their expression by melanocytes could contribute to the anti-melanocyte cellular immune responses that are observed in vitiligo [19,33].

Both vitiligo and normal melanocytes are also capable of expressing MHC class I molecules [31], which could allow interaction with destructive cytotoxic T cells. Indeed, melanocytes have an antigen processing and presenting capability which can make them target cells for T cell-

mediated cytotoxicity [34]. Finally, in perilesional vitiligo biopsies, melanocytes express macrophage markers CD68 and CD36 [32] and reduced levels of membrane regulators of complement activation, including decay acceleration factor and membrane cofactor protein [35], which suggests a vulnerability of these cells to attack by macrophages and the complement system, respectively.

5. Autoantibodies

Melanocyte autoantibodies have been detected in the sera of vitiligo patients at a significantly higher frequency than in healthy individuals [20,36]. They are associated with the extent of vitiligo, being present in 93% of patients with 5-10% of skin area involvement, and in 50% of patients with less than 2% of skin depigmentation [37]. In addition, patients with active vitiligo have increased levels of melanocyte autoantibodies compared to those with stable disease [38,39]. Characterisation of melanocyte autoantibodies has demonstrated that they belong to the subclasses IgG1, IgG2 and IgG3 [40], although studies have also found that IgA levels of melanocyte autoantibodies are associated with disease activity [41]. Several melanocyte-specific autoantibody targets have been identified including tyrosinase [42-44], tyrosinase-related protein (TRP)-1 [45], dopachrome tautomerase (or TRP-2) [46,47], PMEL [48] and GTP-binding protein Rab38 [49].

Autoantibodies against targets not specifically expressed by melanocytes have also been detected in patients with vitiligo including the melanin-concentrating hormone receptor 1, gamma-enolase, alpha-enolase, heat-shock protein 90, osteopontin, ubiquitin-conjugating enzyme, translation-initiation factor 2, tyrosine hydroxylase and laminA [49-51]. In addition, organ-specific autoantibodies, particularly against the thyroid, adrenal glands, gastric parietal cells, and pancreatic islet cells are commonly found in vitiligo patients [52], along with anti-nuclear autoantibodies and IgM-rheumatoid factor [53]. Keratinocyte autoantibodies which correlate with vitiligo extent and activity have been reported [54].

With respect to pathogenicity, vitiligo patient autoantibodies can mediate complement damage and antibody-dependent cellular cytotoxicity against melanocytes and melanoma cells *in vitro* and *in vivo* [55-57]. Passive immunisation of nude mice grafted with human skin has also indicated that IgG from vitiligo patients can induce the destruction of melanocytes [58]. Furthermore, melanocyte autoantibodies from vitiligo patients can induce HLA-DR and ICAM-1 expression on and release of interleukin (IL)-8 from melanocytes [59]. Such changes enhance the antigen-presenting activity of melanocytes allowing antigen-specific immune effector cell attack. More recent work has found that 69% 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 [60]. Finally, melanocyte autoantibodies isolated from vitiligo patients, but not from healthy controls, are able to penetrate cultured melanocytes and trigger them to engage in apoptosis [61].

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6. CD4$^+$helper and CD8$^+$cytotoxic T cells

The first evidence for a possible role for T cells in the pathogenesis of vitiligo came from studies on inflammatory vitiligo [62]. Since then, circulating autoreactive CD8$^+$cytotoxic T that recognise melanocyte antigens (MART1, PMEL and tyrosinase) have been detected in vitiligo patients [33,63-66]. Peripheral CD8$^+$T cells are more prevalent in active cases of vitiligo as compared to stable cases, and their frequency correlates with the extent of depigmentation [53,67]. They also express high levels of the skin-homing receptor cutaneous lymphocyte-associated antigen and display cytotoxic reactivity towards melanocytes [33].

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 [32,68]. Moreover, a significant increase in the number of CD4$^+$and CD8$^+$T cells are detected in the marginal skin in both stable and active vitiligo cases [69]. These perilesional T cells exhibit a predominantly type-1-like cytokine secretion profile of tumour necrosis factor (TNF)-alpha and interferon (IFN)-gamma, the latter enhancing T cell trafficking to the skin by increasing ICAM-1 expression on target cells [70,71]. The majority of infiltrating T cells are activated, as indicated by the expression of the MHC class II antigen HLA-DR [32,68] and the presence of granzyme B$^+$and perforin$^+$cytotoxic T lymphocytes [32]. There is also evidence for down-regulation of the T helper 2 cell-dependent CDw60 molecules in the vitiliginous epidermis. This observation correlates with infiltrating T cells exhibiting a T helper 1 cell-type cytokine production pattern consistent with cell-mediated organ-specific autoimmunity [72].

Using a skin explant model to investigate the effector functions of perilesional CD8$^+$T cells, the latter, which are enriched for cytotoxic T lymphocytes that recognise melanocyte antigens (MART1, PMEL and tyrosinase), infiltrate normally pigmented skin and eradicate melanocytes [19]. The capacity of cytotoxic T cells for damaging melanocytes has also been observed in an experimental murine model of vitiligo: melanocytes were destroyed by CD8$^+$T cells recognising a single H2-Kb-binding peptide derived from dopachrome tautomerase [73].

7. T helper 17 cells

Increased numbers of T helper 17A$^+$cells are found in the leading edge of vitiligo lesions as shown by immunohistochemistry and immunofluorescence [74,75]. Elevated levels of IL-17A mRNA are also present in the same locality [75], evidence that signifies active T helper 17 cells in vitiligo lesions. *In vitro*, T helper 17 cell-related cytokines directly affect melanocyte activity and function, including the down-regulation of melanin production and the shrinkage of melanocytes [74]. In terms of the local cytokine network in the skin, IL-17A dramatically induces production of IL-1beta, IL-6, and TNF-alpha by skin-resident cells such as keratinocytes and fibroblasts [74].

8. Regulatory T cells

Natural Treg cells play a key role in maintaining peripheral tolerance through the active suppression of self-reactive T cell activation and expansion [76], thereby preventing the development of the autoimmune responses. To date, several studies have indicated perturbations in Treg cell numbers and/or function in vitiligo patients [67,77-79]. Such alterations might lead to the reported higher levels and activation of cytotoxic T cells in individuals with the disease [67,77].

Assessment of circulating Tregs by flow cytometric analysis has revealed a decrease in their numbers in vitiligo patients compared to controls [67,77,78]. Reduced peripheral Treg cell numbers have also been reported in early age-of-onset patients (1-20 years) compared to those with late onset vitiligo, and decreased circulating Treg cell counts have been demonstrated in patients with active vitiligo as compared to those with stable disease [67]. Moreover, a striking reduction in the number of Tregs in the marginal and lesional skin of vitiligo patients has been observed [69,80]. Interestingly, some studies have demonstrated that peripheral or lesional skin $CD4^+CD25^+FoxP3^+$Treg cell numbers remain unaltered in vitiligo [81-83], and even that either may be increased [67,84]. Interestingly, discrepancy between the relative abundance of Treg cells present in the circulation of vitiligo patients as compared to their skin was reported to be due to reduced expression of the chemo-attractant CCL22 within vitiligo patient skin so impairing migration of Tregs into the tissue [83].

As well as defects in Treg cell numbers, their function can also be impaired in vitiligo patients. Indeed, the suppressive effects of Tregs in vitiligo cases are significantly reduced as indicated by their impaired ability to inhibit proliferation and cytokine production from autologous $CD8^+$T cells [77,78]. In line with this, the expression of FoxP3 (the dedicated mediator of the genetic program governing Treg cell development and function) in $CD4^+CD25^{hi}$ Tregs is significantly decreased in vitiligo patients compared to controls [67]. Moreover, the mean percentage area of positive immunostaining in skin biopsies and peripheral blood levels of FoxP3 are significantly lower in vitiligo patients compared to controls [85]. Vitiligo area scoring index, vitiligo disease activity and stress score also correlate negatively with FoxP3 levels [85]. The expression of CTLA-4 (a T cell surface molecule involved in regulation of T cell activation) is also decreased in vitiligo patients, an impairment that could perturb the normal suppressive capacity of Treg cells [86]. Furthermore, decreased serum and tissue levels of transforming growth factor (TGF)-beta (important for imposing a Treg cell phenotype) are observed in individuals with vitiligo [87]. Reduced levels of TGF-beta also correlate with increased disease activity [88] and the percentage of involved body area [89]. Moreover, lowered IL-10 (contributes to Treg cell-mediated immunosuppression) levels are present in active cases of vitiligo [88,90]. Finally, and importantly, in a mouse model of vitiligo, the adoptive transfer of melanocyte-specific Tregs was found to induce a lasting remission of the disease [91], thus proposing Treg cells as a potential therapeutic target.

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9. Macrophages

Macrophage infiltration has been demonstrated in vitiligo lesions, with increased numbers present in perilesional compared with normal skin [32,92]. There is evidence that macrophages are involved in the clearing of apoptosed melanocytes from the skin in vitiligo patients [93]. In addition, macrophages expressing activating Fc-gamma receptors have been shown to mediate depigmentation in a mouse model of autoimmune vitiligo [94]. Moreover, macrophage migration inhibitory factor, which is a potent activator of macrophages and is considered to play an important role in cell-mediated immunity, has been found at significantly higher levels in vitiligo patients compared to controls [95].

10. Dendritic cells

Enhanced populations of $CD11c^+$myeloid dermal dendritic cells and $CD207^+$Langerhans cells have been observed in the leading edges of vitiligo lesions [75,96,97]. Dendritic cell-$LAMP^+$and $CD1c^+$sub-populations were also found to be significantly expanded in the lesional edges of vitiligo skin [75]. More recently, dendritic cell-mediated destruction of melanocytes has been demonstrated *in vivo* and *in vitro* [96,98]. This process was related to the release by stressed melanocytes of heat-shock protein 70, a molecule which in turn induced the expression of membrane tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) on dendritic cells as well as the activation of dendritic cell effector functions directed against stressed melanocytes exhibiting elevated TRAIL death receptor expression [96,98].

11. Natural killer cells

Alterations in natural killer (NK) cells have been demonstrated in vitiligo patients indicating a role for them in the pathogenesis of the disease [99]. The percentages of NK cells with activatory receptors, as denoted by the expression of $CD16^+CD56^+$and $CD3^+CD16^+CD56^+$, are significantly increased in vitiligo patients compared with the controls, while the percentage of NK cells expressing the inhibitory receptor $CD158a^+$is significantly reduced.

12. Cytokines

Various studies have implicated cytokine involvement in the pathogenesis of vitiligo [100]. For example, increased serum levels of soluble IL-2 receptor are associated with vitiligo activity, indicating T cell activation [101], and elevated production of IL-6, which can induce ICAM-1 expression on melanocytes thereby facilitating leukocyte interactions, and IL-8, which can attract neutrophils to amplify destructive inflammatory responses, are found in vitiligo patients [102]. In addition, other pro-inflammatory cytokines including IL-1, IL-4, IFN-gamma

and TNF-alpha, which are paracrine inhibitors of melanocytes or initiators of apoptosis, are detected at significantly higher levels in vitiligo patients compared with healthy controls [71, 100,103-105], and IL-17 levels are positively correlated with the extent of body area involvement [106]. In contrast, the level of TGF-beta, required for the maturation of Treg cells, is significantly decreased in vitiligo patients compared with controls [106]. Finally, imbalances of keratinocyte-derived cytokines that affect melanocyte activity and survival are found in vitiligo lesional skin: significantly lower expression of granulocyte-macrophage colony-stimulating factor, stem cell factor and endothelin-1 is detected in depigmented vitiligo lesions compared with normal skin [100].

13. Immuno-regulatory micro RNAs

MicroRNAs (miRNAs) are a class of small non-coding RNAs that negatively regulate gene expression. Abnormal expression of miRNAs which play crucial roles in regulating immunity has been reported in vitiligo. In a mouse model of the disease [107], dysregulated miRNAs included miRNA-146a, which contributes to the regulation of Treg cell function [108] and is implicated in autoimmune disease development in mice [109], as well as miR-191, which mediates in the proliferation and survival of melanocytes [110]. In addition, there is an increase in the expression of immune-regulatory miRNAs miRNA-133b, miRNA-135a, miRNA-9 and miRNA-1 in the lesional skin of vitiligo patients, suggesting an important role for these in vitiligo pathogenesis [111].

14. Treatment modalities

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 [112], has resulted in successful repigmentation responses in vitiligo patients [113,114] 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 [3,115], 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 [116,117].

Psoralen with ultraviolet radiation (PUVA) is used as a second-line therapy for vitiligo [3,118]. 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 [119,120]. 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 [121,122].

Despite the many available therapeutic modalities [115,123], 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.

15. Conclusion

As detailed in this chapter, there is strong evidence for the involvement of autoimmunity in the aetiology and pathogenesis of vitiligo. However, it is most likely that several interacting factors (Figure 1) are responsible for the clinical manifestations of the disease [124]. Indeed, although the evidence for the role of immune-related genes in the aetiology of vitiligo is clear [15], the limited concordance in identical twins [23] indicates that other factors, probably environmental, are also involved in its development, making the disease complex, polygenic, and multi-factorial.

Of note is the finding that oxidative-stress in melanocytes [16-18] results in the secretion of heat-shock protein 70 and chaperoned melanocyte antigens which mediates dendritic cell-activation with the consequential dendritic cell effector functions then playing a role in the destruction of melanocytes [96,125]. This has led to the convergence theory of vitiligo aetiology, which suggests that several factors act synergistically or independently to induce the disappearance of cutaneous melanocytes (Figure 1) [126]. During the elicitation phase of the disease, physical trauma to the skin [126], emotional stresses [12], or imbalances of endogenous neural factors [13], metabolites, cytokines or hormones [87] can lead to oxidative stress within melanocytes, which then respond by actively secreting heat-shock protein 70 and chaperoned melanocyte antigens [125]. In the immune activation stage, these 'danger' signals promote the activation of antigen-presenting dendritic cells with the subsequent activation and recruitment of anti-melanocyte autoreactive cytotoxic T lymphocytes to the skin [19]. Intrinsic damage to melanocytes could, therefore, be the initiating event in vitiligo development followed by a destructive secondary anti-melanocyte immune response from cytotoxic T cells [19,126,127]. Notably, 50% of vitiligo patients experience a Koebner phenomenon, whereby vitiligo develops at a site previously affected by a physical trauma [126]. In addition, different pathogenic mechanisms could account for the various clinical types of vitiligo: pathogenic neural factors are usually related to segmental vitiligo, whereas autoimmunity is most often associated with the non-segmental (generalised) form [2].

As indicated, it is most likely that immune responses in vitiligo are of a secondary nature following melanocyte damage. Indeed, as several vitiligo-associated autoantigens such as tyrosinase and gp100 are located intracellularly, it has been suggested that 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 against these proteins [128,129]. In this scenario, after processing by mature Langerhans cells, antigenic peptides are

presented to T cells which have escaped clonal deletion or to naïve T lymphocytes which are not tolerised to cryptic epitopes [128,129]. Activated cytotoxic T cells can then attack directly melanocytes expressing antigenic peptides in the context MHC class I molecules [31,34], and anti-melanocyte autoantibodies can be produced following the stimulation of B lymphocytes by activated helper T cells [128].

In summary, autoimmunity has an important role to play in vitiligo development with key contributions from anti-melanocyte autoreactive cytotoxic T cells [19], T helper 17 cells [74,75], and Treg cells [77-79].

Author details

Mitesh Dwivedi[1,3*], Naresh C. Laddha[2,3], Anthony P. Weetman[4], Rasheedunnisa Begum[3] and Helen Kemp[4]

*Address all correspondence to: mitesh_dwivedi@yahoo.com

1 C. G. Bhakta Institute of Biotechnology, Uka Tarsadia University, Tarsadi, Surat, Gujarat, India

2 Department of Molecular Biology, Unipath Specialty Laboratory Ltd., Ahmedabad, Gujarat, India

3 Department of Biochemistry, The Maharaja Sayajirao University of Baroda, Vadodara, Gujarat, India

4 Department of Human Metabolism, University of Sheffield, Sheffield, United Kingdom

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