

## Autoantibodies Profile in Vitiligo

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### Abstract

Vitiligo is one of the disease which is yet to understand its pathogenesis, however many studies associate this disease as an autoimmune. Detection of autoimmune cells in the serum, lesional and perilesional area of vitiligo patients gives more insight on the disease mechanism. Presence of autoantibodies against melanocytes antigens in vitiligo patients indicates an autoimmune involvement in the aetiology of the disease. Identification and characterization of vitiligo autoantibodies would pave the way for developing new laboratory test for diagnosis. Studying the autoantibodies profile can give an impression on the disease condition of vitiligo patients. We realized the need of research emphasis in this area as more is yet to be discovered. In this review we give an account on different autoantibodies and their associated autoantigens in vitiligo as another effort of providing an updated data for detail analysis.

**Keywords:** Antibodies; Autoimmunity; Melanocytes; Pigmentation; Vitiligo

### Introduction

Vitiligo is an acquired depigmenting disorder in which melanocytes are destroyed, resulting in patchy depigmentation on skin and mucosal surfaces [1,2]. The worldwide prevalence is range from 0.5–2% [3]. Clinically, vitiligo presents as round or oval white, hypopigmented macules with regular or raised red borders [4]. The disease was classified based on distribution patterns of vitiliginous lesions into focal vitiligo (isolated lesion), segmental vitiligo (unilateral macular lesions which generally cover a dermatome), non-segmental (generalized) vitiligo (most common form, disseminated macules of variable size, usually with a symmetric distribution and a certain predilection for extensor surfaces) [5,6] and universalis vitiligo (severe form that affects more than 80% of the body surface) [4].

The pathogenesis of vitiligo is unclear. although both genetic [7] and environmental factors are the ones implicated as the major cause [8], however, there are other several factors proposed in the pathogenesis of the disease (Figure 1), these include the following, physical trauma [9,10], psychological stress [11], infections [12], neural factors [11,13,14], biochemical factors [15-17], melanocytes growth factors [18], melanocortin hormones [19] and autoimmunity [20].

Most authorities favored the autoimmune causes due to the strong associations of vitiligo with multiple autoimmune diseases; the presence of autoantibodies [21,22] (Table 1), so that autoreactive T lymphocytes against pigment cells supports the theory that there is an autoimmune involvement in the aetiology of the disease [23]. However, even if the specific antibodies to pigment cells or secondary antibodies are not pathogenic, the identification and characterization of their target antigens could be a landmark for uncovering the pathogenic mechanism, formation of autoantibodies [24] and development of biomarkers. In this review we describe some autoantibodies and their associated autoantigens as potential biomarkers for laboratory diagnosis, treatment, monitoring and assessment of vitiligo.

### Anti-Melanocytes

Melanocytes originate from neural crest and are responsible for the synthesis of melanin in melanosomes, membrane-bound organelles [25,26]. They are able to secrete a wide range of signal molecules, including cytokines, Pro-opiomelanocortin (POMC) peptides, catecholamines, and **NO** in response to UV irradiation and other stimuli, for the regulation of variety of skin cells [27]. In active non-segmental vitiligo,

melanocyte cytotoxicity is associated with increase in serum levels of immunoglobulin G (IgG) anti-melanocyte/ vitiligo antibodies (V-IgG) and immunologic markers [28]. IgG anti-melanocyte antibodies were reported to induce melanocyte damage in vitro by a complement-mediated mechanism and antibody-dependent cellular cytotoxicity [29,30]. The melanocytotoxicity could be due to wrong presentation of vitiligo antigens to destructive cytotoxic T cells; this result from abnormal expressions of HLA-DR and increase expression of intercellular adhesion molecule-1 (ICAM-1) on melanocytes by IgG anti-melanocyte antibodies [29,31]. Antibodies to melanocytes occur at a significantly increased frequency in the sera of vitiligo patients when compared with healthy individuals [32]. Interestingly, correlations can also exist between the incidence and level of melanocyte antibodies and both the activity and extent of vitiligo [33]. Identification of anti-melanocyte or vitiligo antibodies against target antigens is useful in developing new diagnostic tests and serves as biomarkers for assessing the progress of the disease [23].

### Anti-thyroid peroxidase (anti-TPO)

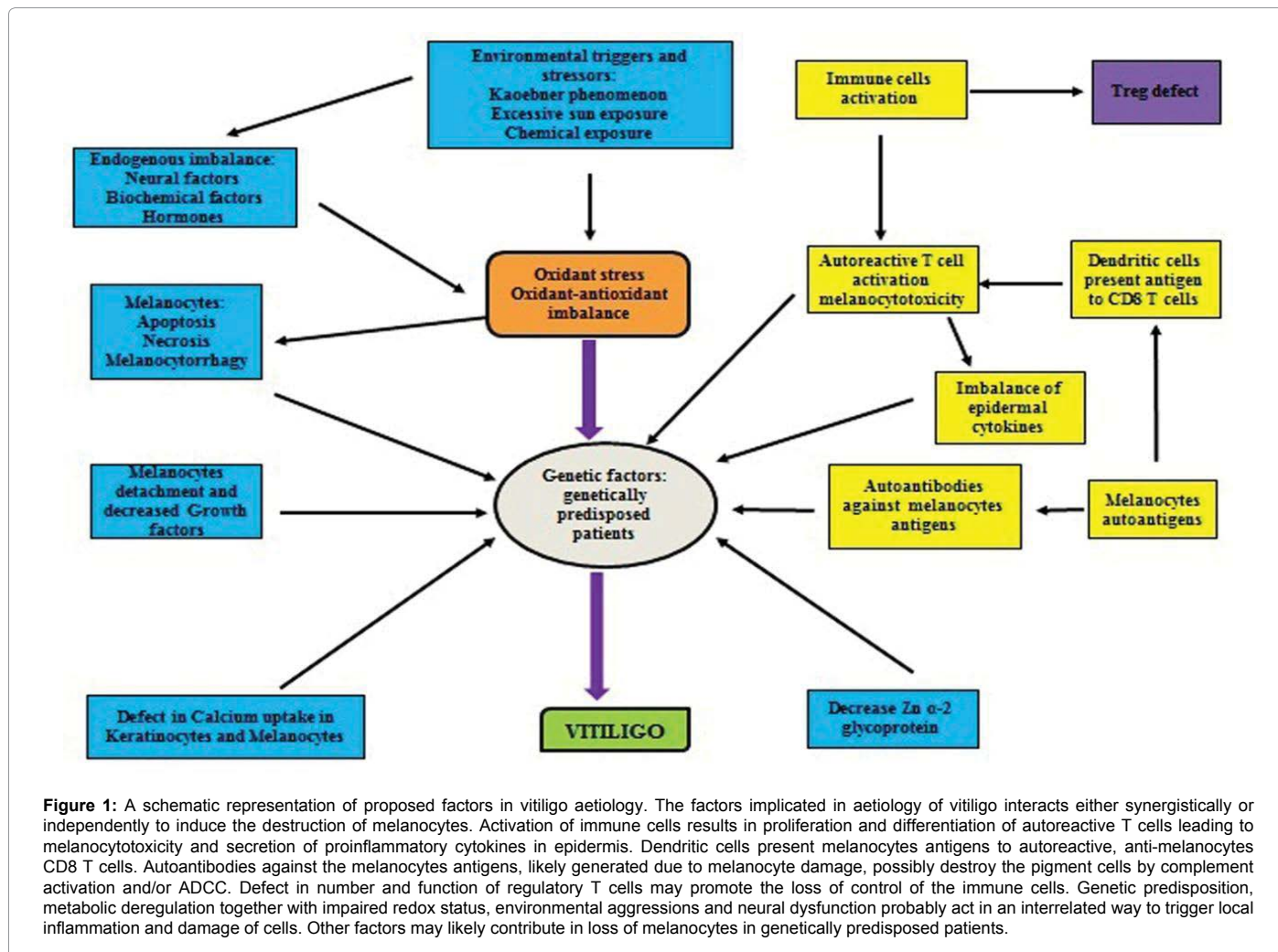
Anti-TPO antibodies are specific for the autoantigen TPO; found in active phase of chronic autoimmune thyroiditis; can be used in monitoring the disease progress in patients with these antibodies [34]. Most of the anti-TPO antibodies are produced by thyroid infiltrating lymphocytes and partly from lymph nodes and bone marrow [35]. In the past decades, many research teams reported the associations between vitiligo and other autoimmune diseases such as thyroid disease and anti-thyroid antibodies [36]. A previous study by Dave et al. reported 31.4% prevalence of thyroid-specific autoantibodies in patients with vitiligo [37]. A more recent study reported a mean prevalence of 20.8% in patients with vitiligo [38]. Again, Kasumagic-Halilovic et al. found higher frequency of anti-TPO in vitiligo patients than control group [39]. Considering these findings vitiligo shows strong association with thyroid autoimmunity, therefore anti-TPO

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**Figure 1:** A schematic representation of proposed factors in vitiligo aetiology. The factors implicated in aetiology of vitiligo interacts either synergistically or independently to induce the destruction of melanocytes. Activation of immune cells results in proliferation and differentiation of autoreactive T cells leading to melanocytotoxicity and secretion of proinflammatory cytokines in epidermis. Dendritic cells present melanocytes antigens to autoreactive, anti-melanocytes CD8 T cells. Autoantibodies against the melanocytes antigens, likely generated due to melanocyte damage, possibly destroy the pigment cells by complement activation and/or ADCC. Defect in number and function of regulatory T cells may promote the loss of control of the immune cells. Genetic predisposition, metabolic deregulation together with impaired redox status, environmental aggressions and neural dysfunction probably act in an interrelated way to trigger local inflammation and damage of cells. Other factors may likely contribute in loss of melanocytes in genetically predisposed patients.

Antibody reactivity	Number of patients with antibodies (%)	Reference
Gastric parietal cells	6/20 (30)	[61]
Thyroid cytoplasm	22/80 (28)	[64]
Thyroid peroxidase	10/20 (50)	[61]
Thyroglobulin	8/20 (40)	[61]
Tyrosinase	5/46 (10.9)	[65]
TYRP1	8/84 (9.5)	[24]
TYRP2	20/30 (67)	[60]
Adrenal gland	3/80 (4)	[64]
Pancreatic islet cells	7/96 (7.2)	[36]
Anti-nuclear antibody	4/55 (7.3)	[32]
IgM-rheumatoid factor	6/55 (10.8)	[32]
Lamin A	24/84 (28.6)	[24]
MCHR1	24/145 (16.55)	[66]
γ-enolase	4/53 (8)	[67]
α-enolase	5/53 (9)	[67]
HSP90	7/53 (13)	[67]
HSP70	16/60 (26)	[68]
Fibrin beta	16/60 (26)	[68]
Osteopontin	5/53 (9)	[67]
Ubiquitin-conjugating enzyme	8/53 (15)	[67]
Translation-initiation factor 2	3/53 (6)	[67]

**Table 1:** Some of the antibodies detected in vitiligo patients.

detection in vitiligo patients could be a useful markers for assessment of the disease. In this case more in-depth studies are required to give detail information.

### Anti-melanocortin 1 receptor (MC1R)

The melanocortin peptide α-melanocyte-stimulating hormone (MSH) is an important regulatory agent in skin pigmentation, inflammatory modulation and response to stress [19,40]. The α-MSH binds to MC1R on the melanocyte [41] to increase tyrosinase activity and eumelanin production; this action could lead to regulation of melanocytes, skin pigmentation, NO production and release of other signalling molecules from melanocytes [41]. Moreover, Pichler et al. reported that α-MSH levels were significantly lower in vitiligo patients compared to normal individuals [42]. Since the expression level of α-MSH in the melanocytes from lesion and perilesion area of vitiligo skin are lower than that from normal skin [43]. The proportion of α-MSH immuno-positive melanocytes is significantly reduced in the lesional and perilesional skin of vitiligo patients compared to controls [44]. Autoantibodies against MC1R are rare or absent in sera of vitiligo patients [45].

### Melanin concentrating hormones receptor (MCHR)-binding antibodies

MCHR1 has been identified as a B cell autoantigen in vitiligo; the

antibodies against this receptor are detected in binding and function-blocking assays [46]. A previous study has shown they can block the stimulation of the receptor by MCH in a heterologous cell line [47]. Noteworthy, the MCH/ MCHR signalling pathway is critical in regulating melanocyte function along with  $\alpha$ -MSH and the MC1R [48], any action by MCHR1 antibodies to interfere in the normal functioning of the receptor could change the pigment cell behavior. However, the effect of these antibodies on the MCHR1 in melanocytes either *in vitro* or *in vivo* is obscure [23]. Few years back, the technique of peptide phage-display has identified the MCHR1 as a target of vitiligo patient antibodies [49]. Moreover, MCHR autoantibodies were found at a significantly increased frequency in the vitiligo patient group compared to healthy controls. In addition, vitiligo patient IgGs were tested for MCHR autoantibodies that could mediate antibody-dependent cell-mediated cytotoxicity via the receptor [47]. More study on MCHR1 antibodies is required to affirm their role in vitiligo aetiology and could be reliable biomarkers for vitiligo diagnosis in future.

### Melanoma antigen recognized by T-cells (MART)

MART is a protein antigen that is found on the surface of melanocytes. Antibodies against this antigen are used in the medical specialty of anatomic pathology in order to recognize cells of melanocytic differentiation, useful for the diagnosis of a melanoma [4]. A study showed that serum level of melanocyte antibody in children with vitiligo was significantly higher than that in normal subjects and MART-1 was found binding to specific MART-1 antibody [50]. This indicates that MART-1 antibody may be useful in monitoring the autoimmune mechanism in patients with vitiligo. However, Bam and Bagchi reported that MART-1 transcript is not detected in the PBMCs of vitiligo patients but is detected in healthy controls [51]. The non-expression of MART1 may be plausibly implicated for the tolerance breakdown and subsequent induction of autoimmunity in the vitiligo patients. Antibody against MART-1 requires further investigation, as it may potentially give an insight on autoimmune mechanism in vitiligo patients.

### Lamin A (VIT 75) autoantibody

Vitiligo autoantigen VIT75 is identified as Lamin A in Vitiligo. VIT75 is melanocyte membrane antigen that had been observed, but not identified until recently, indeed, its immunopathogenic role in vitiligo remains unknown [24]. However, anti-lamin antibodies are detected in sera in a range of autoimmune diseases [52]; although the process on how these antibodies are induced *in vivo* is yet to be clear. Interestingly, majority of vitiligo patients with anti-lamin A had at least one autoimmune disorder; the prevalence rate and titers of the antibodies are higher than in the patients without autoimmune disease or healthy controls [24]. Furthermore, previous study showed that 83% of vitiligo patients had the antibodies against VIT75 while only 7% of controls showed reactivity against it [53]. Henceforth, anti-lamin A antibody may likely be a potential marker of non-segmented vitiligo with autoimmune disease [24]. Here the use of serological proteome analysis to target autoantibodies in vitiligo patients is highly encouraged to give more insight.

### Tyrosine Hydroxylase (TH) antibody

TH was generally accepted as autoantigen in vitiligo using phage-display technology [54]. TH was suggested to play role in melanin synthesis by supplying a substrate L-dopa for tyrosinase which subsequently converts L-tyrosine to dopaquinone, a precursor of melanin [55]. Although there are controversies on the presence of TH in melanocytes, existing knowledge indicates that the TH mRNA

has been found in human epidermal melanocytes and this enzyme is located on the melanosomal membrane together with tyrosinase. In contrast, Kågedal et al. reported that the levels of TH mRNA in several melanocytes were insignificant or undetectable [56]. However, TH antibodies were elevated in patients with active vitiligo and the antibodies were reported to target TH in non-segmental vitiligo [54]. Also Kemp and his co-workers reported a significant increase in the prevalence of TH antibodies in patients with non-segmental vitiligo when compared with controls [54]. In addition, TH antibodies were not found in patients with segmental vitiligo, healthy controls and patients with other autoimmune diseases without concomitant vitiligo [54]. Moreover, a study on TH epitopes recognized by TH antibodies in patients with vitiligo and alopecia areata (AA) reported that TH antibodies from patients with vitiligo or AA can recognize identical epitopes [57].

### Tyrosine related protein (TRP-2)

Tyrosinase and tyrosinase associated protein 1 and protein 2 catalyze the biochemical steps in the biosynthesis of melanin [4]. The TRP2 protects human against oxidative stress by increasing glutathione levels and by reducing the toxicity of quinones and DNA damage induced by free radicals [58]. Several melanosome glycoproteins have been shown to be antigenic in human. A previous study on antibody responses to a melanocyte autoantigen, TRP-2, found that this autoantigen is immunogenic in human [59]. The TRP-2 antibody responses provide a linkage between autoimmune responses by vitiligo and melanoma patients responding to immunotherapy who have induced hypopigmentation [60]. However a more recent study reported that TRP-2 transcripts from peripheral blood mononuclear cells (PBMCs) are absent in vitiligo patients but present in healthy individuals [51]. Considering these findings, studies on Anti-TRP-2 are inconsistent; therefore studies to confirm its reliability as potential biomarker for development of new diagnostic test in vitiligo could be a good approach.

### Other Antibodies

Circulating organ-specific autoantibodies particularly to the thyroid, adrenal glands, gastric parietal cells, and pancreatic islet cells are commonly detected in the sera of vitiligo patients [61]. Moreover, antinuclear antibody and IgM-rheumatoid factor have been detected at a significant frequency in vitiligo patients [32]. Anti-keratinocyte intracellular antibodies that correlate with disease extent and activity have also been detected in vitiligo patients [62]. Tyrosinase-related protein 1 (TYRP1) is a critical enzyme for the correct trafficking of tyrosinase to melanosomes [63]. In addition, autoantibodies against TYRP1 are also suggested in vitiligo patients (Table 1).

### Conclusion

It is obvious there is strong indication that autoantibodies are playing significant role in vitiligo pathogenesis. Although there are some disputed findings, however most of the studies indicate the presence of autoantibodies in vitiligo patients, therefore the use of these antibodies for development of new laboratory test for diagnosis is indeed a good approach. The antibodies in vitiligo can serve as potential biomarkers for monitoring and assessment of autoimmune diseases in vitiligo patients. In-depth researches in this area could likely give a good conclusion on the pathogenic mechanism of vitiligo in autoimmune diseases. Certainly, there are more to discover in vitiligo pathogenesis.

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