REVIEW

Potential Role of Neurogenic Inflammatory Factors in the Pathogenesis of Vitiligo

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Background: **Vitiligo is a highly complex multifactorial condition of the skin that has an unclear mechanism of pathogenesis.**

Objective: **This review summarizes the role of various neurogenic inflammatory factors significantly upregulated in vitiligo.**

Methods: **A literature review was conducted of all pertinent data regarding neuropeptides that are altered in vitiligo and their possible role in the destruction of melanocytes.**

Results: **The close associations between the skin, immune system, and nervous system, along with specific changes demonstrated in vitiligo patients, support a pathogenic mechanism of vitiligo that involves neuroimmunologic factors, the release of which can be governed by mental stress.**

Conclusion: **Neuropeptides and nerve growth factors are critical regulators of emotional response and may precipitate the onset and development of vitiligo in certain predisposed individuals. More studies are required to investigate whether a direct link exists between genetics, mental stress, and neurogenic factors in vitiligo.**

Renseignements de base: **Le vitiligo est une anomalie de la pigmentation de la peau ayant une étiologie multifactorielle très complexe dont le mécanisme de pathogenèse n'est pas clair.**

Objectif: **Ce résumé présente brièvement le rôle de divers facteurs d'inflammations neurogènes régulés à la hausse de façon significative dans le vitiligo.**

Méthodes: **Cet article comprend une analyse documentaire de toutes les données pertinentes sur les neuropeptides qui sont modifiés dans le vitiligo et leur rôle possible dans la destruction des mélanocytes.**

Résultats: **Les associations étroites entre la peau, le système immunitaire, et le système nerveux, avec des modifications particulières démontrées chez les patients atteints de vitiligo, appuient un mécanisme pathogène de vitiligo qui met en jeu des facteurs neuro-immunologiques dont la libération peut être régie par la tension mentale.**

Conclusion: **Les neuropeptides et des facteurs de croissance nerveuse sont des régulateurs essentiels de la réponse émotionnelle et peuvent précipiter l'apparition et le développement du vitiligo chez certaines personnes prédisposées. D'autres études sont nécessaires pour déterminer s'il existe un lien direct entre la génétique, la tension mentale, et les facteurs neurogènes du vitiligo.**

VITILIGO is an acquired pigmentation disorder in which melanocytes, the principle pigment-producing cells in humans, are destroyed. With a worldwide incidence of 0.5 to 1%, vitiligo can be a highly disfiguring disorder. The resulting depigmentation can affect the retinal epithelium, the skin, the hair, and the mucous membranes.[1–3] Although vitiligo is traditionally viewed as a minor disease, it has been reported to have a severe impact on the psychological well-being of the affected individuals, resulting in impaired social interactions and decreased quality of life.[4–7] In addition to the cosmetic and psychosocial implications, there is increasing evidence of association with other autoimmune diseases, such as systemic lupus erythematosus, hypothyroidism, diabetes, and various disorders of the nervous system.[8–16] Therefore, vitiligo has a major impact on the well-being of the affected individuals.

The pathogenesis of vitiligo is poorly understood. The main reason lies in the multifactorial nature of the disease, which progresses as a result of the interplay between multiple genes and environmental factors. Several prevailing pathogenic theories have dominated the mainstream literature: (1) the autoimmune theory[17]; (2) the neural

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hypothesis[18]; (3) the oxidative and redox imbalance theory (which overlaps with the neural hypothesis)[19]; and (4) the melanocytorrhagy or "intrinsic adhesion defect" theory.[20] Although each theory has its own proponents, the autoimmune hypothesis arguably has the most advocates and experimental support. However, it is likely that the pathogenesis of vitiligo involves a combination of multiple proposed mechanisms. Accumulating research has revealed intricate connections and bidirectional crosstalk between the immune system and the nervous system[21–23] and the impact they may have on the survival and integrity of melanocytes in vitiligo skin. It is well established that immune-related cells in the skin (such as lymphocytes, macrophages, natural killer cells, and keratinocytes) express receptors for neurotransmitters and neuropeptides.[24–28] This review highlights findings from the literature that support a pathogenic role by stress-induced neurogenic inflammatory factors in the development of vitiligo.

Evidence of Neuroendocrine Imbalance in Vitiligo

Studies have demonstrated in vitiligo lesional skin altered numbers and distribution of nerve fibers, including those that secrete neuropeptide Y (NPY) and calcitonin gene–related peptide (CGRP)[29,30] and those that are immunoreactive for the low affinity (p75) nerve growth factor receptor (NGFr-IR).[31] Significantly elevated levels of NPY in the plasma and tissue fluids of vitiligo patients have also been observed.[32] Furthermore, it has been documented that the catecholamine neurotransmitters such as dopamine, epinephrine, and norepinephrine are significantly elevated in the serum and urine of vitiligo patients.[33–37]

Role of Mental Stress in Vitiligo

There is accumulating evidence of a strong association between mental stress and the onset or progression of vitiligo. A case-control study in 2004 on children afflicted with vitiligo and psoriasis showed that the onset of vitiligo was associated with psychological factors.[38] Another case-control study done by Manolache and Benea demonstrated that vitiligo patients are much more likely (odds ratio of 6.81) to encounter stressful events in their life.[39] Their study also revealed that patients were much more likely to experience one stressful event before the onset of vitiligo. Furthermore, it has been suggested that patients with alexithymia (deficiency in the ability to express emotions) and those with poor social support are more susceptible to vitiligo.[40]

Mental stress and other psychological factors have been widely implicated in the initiation and exacerbation of autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, diabetes, and various dermatoses.[41] Furthermore, it has been suggested that the stress-associated exacerbation of autoimmune or inflammatory disorders is mediated through neurotransmitters and hormones.[42]

An important consequence of mental stress is through its effect on the secretion of catecholamines via stimulation of the hypothalamic-pituitary-adrenal (HPA) axis,[42,43] which consists of a set of complex interactions between the hypothalamus, pituitary gland, and adrenal glands. Systemically, psychological and emotional disturbances can trigger the production and release of corticotrophin-releasing hormone (CRH) by the hypothalamus, which in turn stimulates the release of adrenocorticotropic hormone (ACTH) by the pituitary gland. ACTH can act on the adrenal gland to produce various corticosteroids and catecholamines. More importantly, in addition to systemic effects, the HPA axis has been shown to play a crucial regulatory role in the local microenvironment of the skin, where ACTH, CRH, and CRH receptors are involved.[44] Moreover, melanocyte development and pigment production are directly regulated by local sympathetic adrenergic innervations, an increased activity of which has been shown in vitiligo lesions.[45–47]

In addition to catecholamines, other neural-inflammatory mediators implicated in vitiligo pathogenesis, such as NPY, CGRP, nerve growth factor (NGF), and NGF receptors, are also strongly influenced by mental stress.[48–54] NPY is known to be concentrated in the hypothalamus in the central nervous system. In the peripheral nervous system, NPY is mainly present in the sympathetic innervations and coreleased with catecholamines on nerve stimulation by mental stress.[48] In addition, NPY has been suggested to play a regulatory role in the maintenance of emotional homeostasis by either stimulating or suppressing the HPA axis depending on the plasma concentration of epinephrine and norepinephrine.[55,56] Therefore, NPY is an important molecule involved in the HPA axis in mediating stress and anxiety.

Stress-induced upregulation of NGFs and their corresponding receptors is known to promote various neurogenic inflammatory processes by stimulating the secretion of proinflammatory neuropeptides such as CGRP and substance P (SP).[49,54] Joachim and colleagues demonstrated that both mental stress and administration of NGF were able to significantly induce the growth of CGRP and SP-positive nerve fibers in murine skin and that the application of anti-NGF successfully abrogated the response.[49] In addition, CGRP has been shown to further stimulate the

HPA axis to produce corticosteroid hormones, such as cortisol, which in turn may induce the production of epinephrine and norepinephrine.[57] In the context of vitiligo, increased growth of CGRP-positive nerve fibers in the skin may be stimulated by the release of NGF as a result of mental stress. In addition, being one of the most potent vasodilators known,[58] CGRP may also be upregulated in response to vasoconstriction evoked by other stress-induced neuropeptides, such as NPY and catecholamines.[59]

Neurogenic Inflammatory Response in Vitiligo

Numerous studies demonstrate that neurogenic factors strongly influenced by mental stress can directly and/or indirectly influence the survival and structural integrity of melanocytes. The following summarizes the evidence supporting a potential pathogenic role played by the following neurogenic factors: NPY, CGRP, catecholamines, and NGFs and NGF receptors. In general, the potential mechanisms through which these factors lead to melanocyte destruction are (1) nonspecific direct cytotoxicity to melanocytes and (2) the initiation and propagation of local and systemic immune or inflammatory reaction, including a specific adaptive immune response against melanocytes (Figure 1, Figure 2, Figure 3, and Figure 4).

Neuropeptide Y

Widely distributed in both the peripheral and the central nervous system, NPY is a neurotransmitter with diverse functions.[60] It is a stress hormone and a potent vasoconstrictor. It has been implicated in the regulation of food intake, memory, and neuroendocrine balance.[61–65] NPY can influence the survival of melanocytes by several potential mechanisms, including indirect activation of adaptive immune response and through formation of reactive oxygen species (ROS) (see Figure 1).

There is substantial evidence of NPY playing an important role in regulating the function of cells involved in innate and adaptive immunity, such as monocytes, polymorphonuclear leukocytes (PMNs), lymphocytes, and antigen-presenting cells (APCs). In addition to enhancing the phagocytosis capabilities of APCs, such as dendritic cells (DCs), NPY has been shown to directly stimulate the production and release of ROS in PMNs and macrophages, both directly by binding to Y1 and Y5 receptors and indirectly by stimulation of the central nervous system, which has been demonstrated in mice.[66–70] ROS may also be generated as a result of the vasoconstrictor effects exerted by NPY on endothelial cells in the skin capillary system. Vasoconstriction activates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in endothelial cells and phagocytes, which catalyzes the formation of ROS.[71]

Elevated levels of oxygen radicals and peroxide have been well documented in the dermis of vitiligo patients. It has been reported that ROS can cause destruction of melanocytes via direct cytotoxic effects, deactivation of critical enzymes (ie, catalase and acetylcholinesterase), and alteration of melanocytic structural antigens or "neoantigens," which triggers further specific adaptive immune response against melanocytes.[72–74]

There is substantial evidence of NPY playing an important role in regulating the production of cytokines by macrophages, PMNs, and lymphocytes. This effect of NPY is exerted through its binding to various types of adrenoceptors (ARs) present on these cells. Through its stimulation of ARs, NPY can stimulate the production of proinflammatory cytokines in lymphocytes and PMNs, such as interleukin (IL)-1β, IL-6, interferon-γ (IFN-γ), and tumor necrosis factor α (TNF-α).[75–78] All of these cytokines were previously reported to be elevated in the serum and lesional skin of vitiligo patients.[79,80] It is noted that NPY's effects on the secretion of proinflammatory cytokines are not universally accepted, with some reports demonstrating an increased production of IFN-γ and IL-2, skewing the immune response toward the T-helper (Th)1 pathway, whereas others reported the opposite effect, in that NPY suppresses the Th1 pathway and instead promotes the production of IL-4, shifting to a Th2-type response.[77,81] Therefore, the precise role of NPY in the cytokine dysregulation observed in vitiligo patients remains to be further clarified.

The presence of leukocyte infiltrates—T cells, Langerhans cells (LCs), and macrophages—in the lesional and perilesional skin of vitiligo patients has been well-documented.[82–86] NPY may play a role in this because it has been shown to have a profound impact on the trafficking of leukocytes, especially activated monocytes and T lymphocytes.[70,78,87,88] These observations, when combined with the evidence of increased dermal NPY-positive nerve fibers and elevated levels of NPY in the plasma of vitiligo patients, strongly suggest a pathogenic role of NPY in the recruitment of immune cells in vitiligo.

Calcitonin Gene–Related Peptide

Another neural peptide secreted by primary afferent sensory neurons in the skin, CGRP,[89] also participates in the communication between the nervous and immune

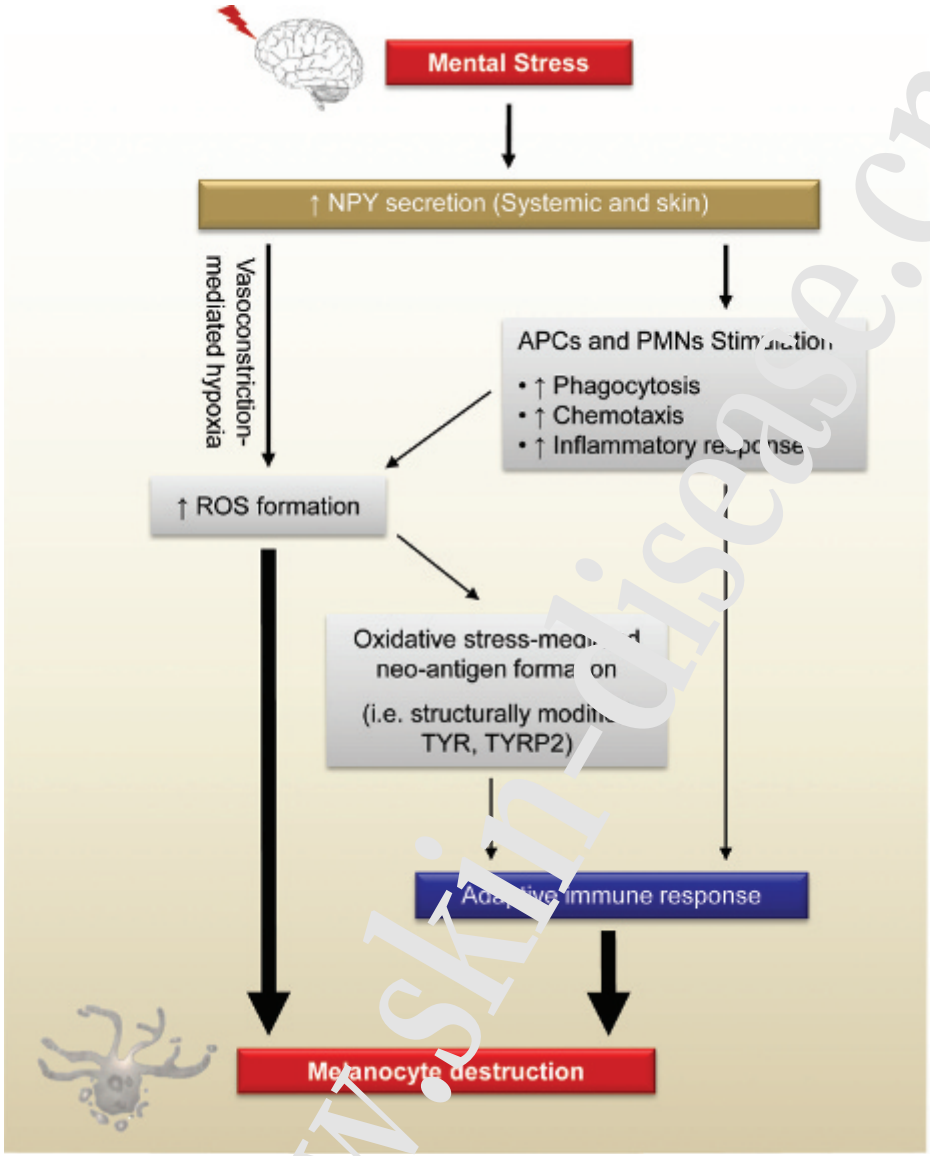

Figure 1. Proposed mechanism of neuropeptide Y–mediated melanocyte destruction. Increased release of neuropeptide Y as a result of emotional stress in genetically predisposed individuals may trigger inflammatory responses initiated by antigen-presenting cells and polymorphonuclear leukocytes. The consequences of such inflammation are increased proinflammatory cytokines and reactive oxygen species, which may cause direct melanocyte cytotoxicity. Chronic inflammatory responses would also trigger specific adaptive immune responses against melanocytes in general. APC = antigen-presenting cell; NPY = neuropeptide Y; PMN = polymorphonuclear leukocyte; ROS = reactive oxygen species; TYR = tyrosinase; TYRP2 = tyrosinase-related protein 2.

systems and potentially influences the survival of melanocytes (see Figure 2). CGRP has been shown to be associated with a variety of hypersensitivities and neurogenic diseases, such as the common migraine, temporomandibular joint disorder, rhinosinusitis, and atopic dermatitis.[90–92] More interestingly, many immune and nonimmune cells of the skin, such as mast cells, neutrophils, LCs, lymphocytes, Schwann cells, keratinocytes, and fibroblasts, express CGRP receptors, which, when stimulated, could result in inflammatory responses, possibly through the activation of the mitogen-activated protein (MAP) kinase signaling pathways.[78,93,94] For example, Levite and colleagues demonstrated in several studies that in addition to enhancing the adhesion capability of lymphocytes to the extracellular matrix, CGRP, along with other neuropeptides, can stimulate the secretion of various proinflammatory cytokines by naive and mature Th1 and Th2 antigen-specific T cells, suggesting that CGRP may augment both Th1 and Th2 adaptive immune activities.[78,94]

The effect that CGRP has on traditionally nonimmune cells can be best demonstrated in a study done by Vause and Durham on peripheral glial cells and Schwann cells, which, when cultured with the CGRP, produced drastically elevated levels of proinflammatory cytokines such as IL-1, 6, IFN-γ, and TNF-α.[95] Furthermore, keratinocytes in the presence of CGRP exhibited an increased proliferation rate and production of IL-8, which is a potent chemoattractant for macrophages and neutrophils.[96]

Given that LCs are closely associated with CGRP-positive nerve fibers in the skin,[97] and there is evidence

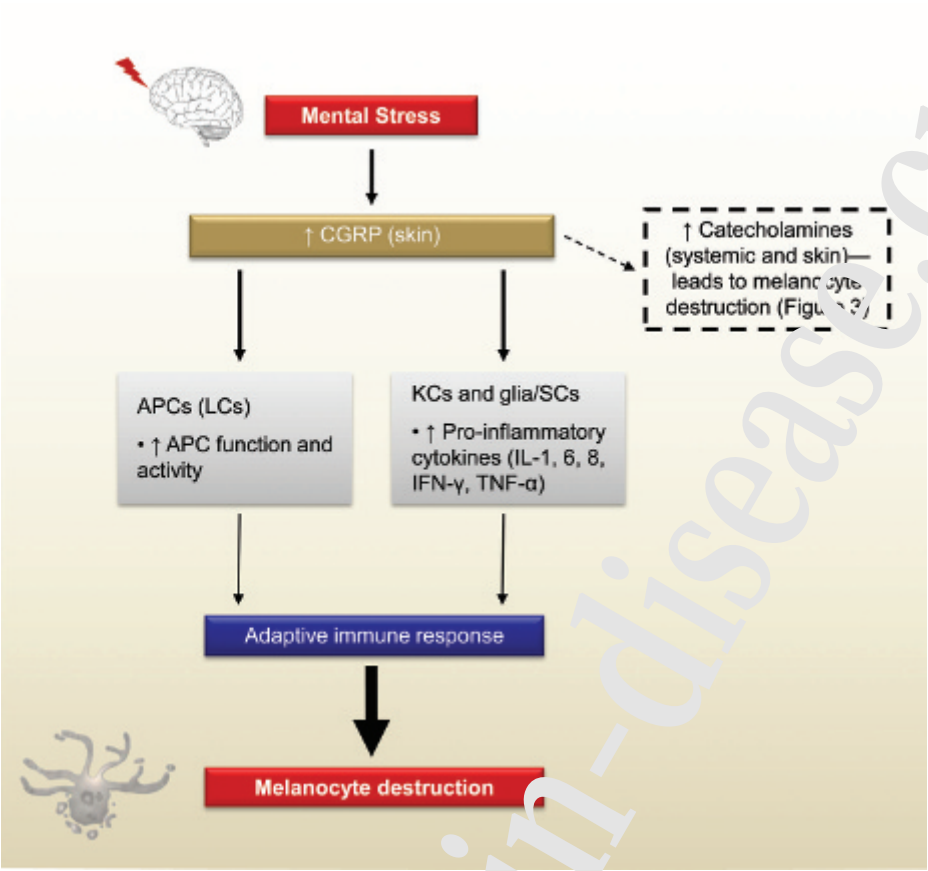

Figure 2. Proposed mechanism of calcitonin gene–related peptide (CGRP)-mediated melanocyte destruction. Emotional stress and anxiety can trigger increased production and release of CGRPs from sympathetic nerve endings in the skin. Chronic release of CGRP may trigger local and systemic inflammation by direct activation of keratinocytes, Langerhans cells, and glial cells in the skin. In addition, CGRP can induce the release of catecholamines through stimulation of the hypothalamus-pituitary-adrenal axis. APC = antigen-presenting cell; IFN-γ = interferon-γ; IL = inerleukin; KC = keratinocyte; LC = Langerhans cell; SC = Schwann cell; TNF-α = tumor necrosis factor α.

that CGRP augments the antigen-pr[illegible]bility of LCs,[98] it is possible that the coordination a[illegible]timulation of LCs by CGRP represent an early st[illegible]ading to the melanocyte-specific adaptive immune responses observed in vitiligo. Another potential mechanism through which CGRP may influence melanocyte survival is via its ability to stimulate catecholamine secretion in vitiligo[57] (see Figure 3).

Catecholamines

The death of melanocytes in vitiligo has been attributed to increased oxidative stress caused by the accumulation of sympathetic catecholamine neurotransmitters and their metabolites (see Figure 3). For example, multiple studies have demonstrated increased urinary and serum levels of dopamine, epinephrine, and norepinephrine in vitiligo patients compared to controls.[33–37] In addition, the oxidation products of epinephrine and norepinephrine, such as homovanillic acid (HVA) and vanillylmandelic acid (VMA), were also found in significantly elevated levels in the urine of vitiligo patients.[33,35] The main consequence of catecholamine accumulation may be the production of peroxide and toxic oxygen radicals as a result of (1) metabolic breakdown of catecholamines by monoamine oxidases, which has been observed to be upregulated in vitiligo lesional skin,[36,99] and (2) vasoconstriction and subsequent hypoxia induced by norepinephrine, which has also been shown to activate monoamine oxidases, possibly as a regulatory mechanism for its own degradation.[100]

Recent studies have shown that the monoamine neurotransmitters, especially epinephrine and norepinephrine, influence immune responses primarily via direct binding to high-affinity α and β adrenoreceptors that are present on most leukocytes. It has been demonstrated that epinephrine-treated DCs can elicit the production of various cytokines by T lymphocytes, such as IL-4, IL-10, IL-12, and, most notably, IL-17, a finding that implicated epinephrine in skewing the immune responses toward either the Th2 or the Th17 pathway.[101] The Th17 pathway has been implicated in the initiation and progression of autoimmune diseases.[102–107] IL-17 is a potent inducer of other proinflammatory cytokines such as IL-1, IL-6, and TNF-α.[108–111] Moreover, a significantly elevated level of IL-17 has been observed in both the serum and the tissue fluid of vitiligo patients.[112]

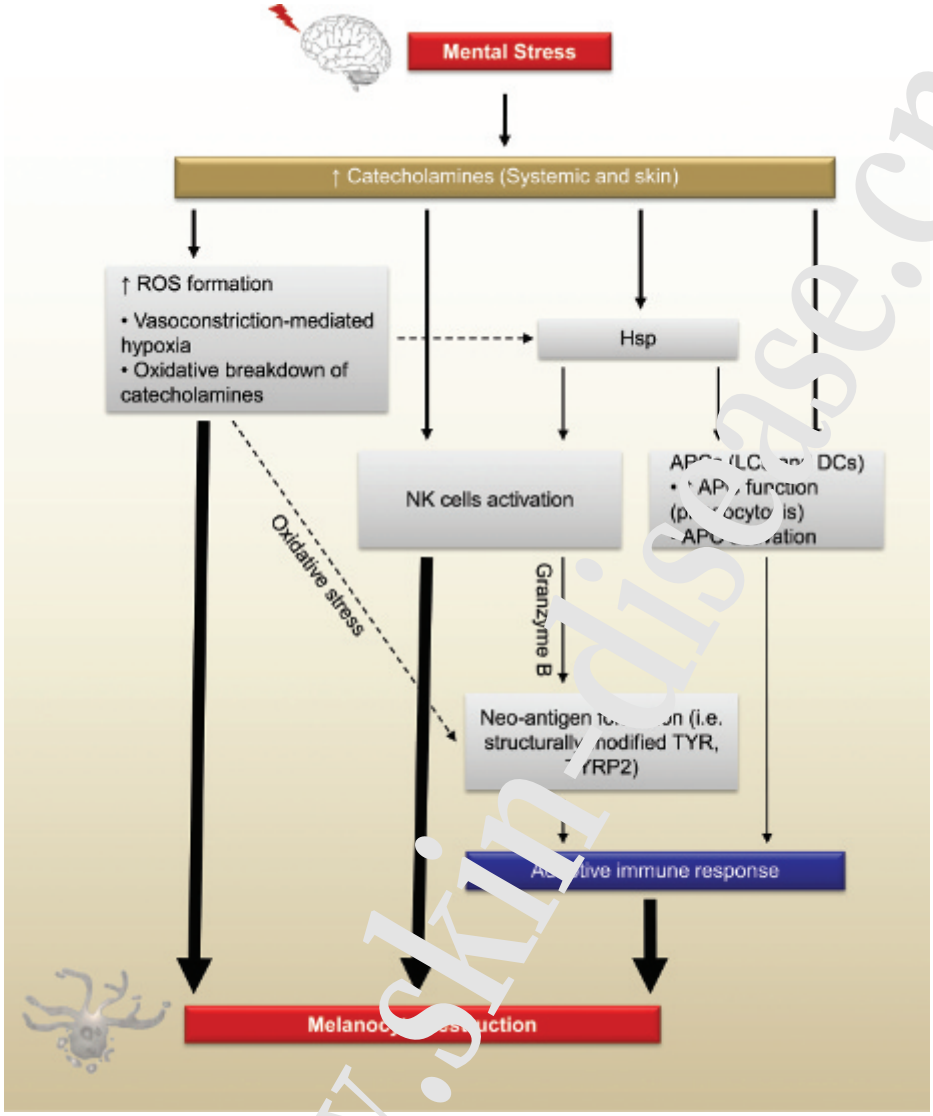

Figure 3. Proposed mechanism of catecholamine-mediated melanocyte destruction. Emotional stress can directly stimulate the hypothalamus-pituitary-adrenal axis to release catecholamines from the adrenal gland as well as adrenergic nerve endings in the skin. The increased levels of catecholamines and their metabolic products may mediate immune responses via several pathways: (1) direct stimulation and activation of natural killer cells, which may cause direct cytotoxicity of melanocytes through granzyme B–mediated apoptosis and possible formation of neoantigens; (2) stimulate the release of heat shock proteins by melanocytes, which may then trigger an inflammatory response involving the recruitment and activation of antigen-presenting cells followed by the development of adaptive immune responses; (3) direct activation of antigen-presenting cells such as dendritic cells and Langerhans cells; and (4) formation and accumulation of reactive oxygen species, which, besides causing direct melanocyte destruction, would also trigger an inflammatory cascade, leading to the activation of adaptive immunity. APC = antigen-presenting cell; DC = dendritic cell; Hsp = heat shock protein; LC = Langerhans cell; NK = natural killer; ROS = reactive oxygen species; TYR = tyrosinase; TYRP2 = tyrosinase-related protein 2.

A study by Dimitrov and colleagues showed that epinephrine can selectively recruit and mobilize cytotoxic leukocytes, such as $CD8^+$ T cells, $CD3^+CD56^+$ natural killer T (NKT)-like cells, and natural killer cells.[113] Both cytotoxic $CD8^+$ T cells and natural killer cells have been implicated as playing a direct role in the destruction of melanocytes in vitiligo as they were found in a significantly increased number in either the blood or the lesional skin of vitiligo patients.[82,114]

There is evidence that norepinephrine may also play a prominent role during the immune response, such as in augmenting antigen uptake by macrophages and stimulating natural killer cells. Norepinephrine has been shown to induce increased endocytosis by DCs via α_2-adrenoreceptor stimulation and activation of the PI3K and ERK1/2 intracellular signaling pathways.[115] Norepinephrine was also able to increase the cytotoxicity of natural killer cells, possibly by direct stimulation via α-adrenoreceptors.[116,117]

Catecholamines have previously been demonstrated to induce intracellular heat shock protein (Hsp)72 in tissues via direct stimulation of α_2-adrenergic receptors.[118–121] Hsps are stress-inducible proteins present in all cells and are crucial in the induction of innate immunity, especially in response against cancer.[122–124] Hsps are known to enhance both innate and adaptive immunologic responses by stimulating the proliferation of DCs and cytotoxic T cells as well as the release of proinflammatory cytokines via a calcium-dependent pathway.[125–131] The Hsp70 family is also known to enhance the cytotoxic activity of natural killer cells[122,132] and induce the secretion of proinflammatory cytokines and proteases, such as IFN-γ and granzyme B, which, besides direct cytotoxic effects, has also been

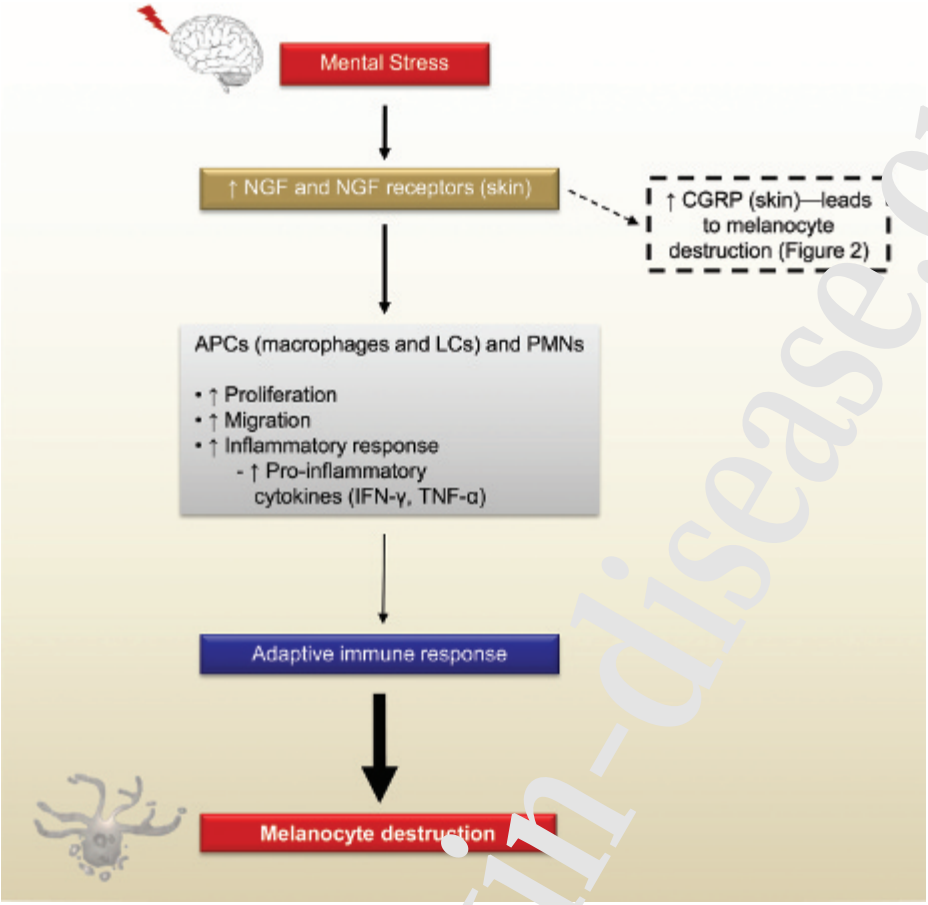

Figure 4. Proposed mechanism of nerve growth factor (NGF)-mediated melanocyte destruction. NGFs are suggested to be important mediators of neurogenic inflammation in many autoimmune diseases. NGFs have been demonstrated to play a critical role in the development of both cell-mediated and humoral adaptive immunity and are especially important in the maintenance of immunologic memory. In addition to the direct effect on the activity of immune cells, NGFs are also potent stimulants for the growth of peptidergic nerve endings in the skin and thus are able to induce the release of additional neuropeptides, which include CGRP. APC = antigen-presenting cell; CGRP = calcitonin gene–related peptide; IFN-γ = interferon-γ; LC = Langerhans cell; PMN = polymorphonuclear leukocyte; TNF-α = tumor necrosis factor α.

implicated in the generation of "neoantigens" in autoimmune diseases.[74,133] Recent studies have shown that Hsps may play a role in the pathogenesis of vitiligo. Histologic studies have revealed consistent differential expression of Hsp70 in the lesional and perilesional skin of vitiligo patients.[134] Denman and colleagues recently demonstrated in a mouse model of autoimmune vitiligo that gene gun vaccination of expression vectors containing tyrosinase-related protein 2 (Trp-2) along with Hsp70 significantly accelerated the depigmentation process compared to control (Trp-2 only) vectors.[135] Hsps are also expressed in times of hypoxia and oxidative stress to augment the activity of antioxidative enzymes to protect cell viability.[136–139] In the skin, Hsp70 can be readily induced in fibroblasts with peroxides.[140,141] Interestingly, Kroll and colleagues demonstrated in their study that oxidative stress (in the form of the chemical 4-tertiary butyl phenol) was able to induce the secretion of Hsp70 by melanocytes cultured in vitro, which in turn induced the upregulation of membrane tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) expression and subsequently enhanced DC-mediated killing of melanocytes.[86] This suggests that in the context of vitiligo, the accumulation of catecholamines will not only directly induce the expression of Hsps in melanocytes via adrenoreceptor interaction[142] but may also stimulate the release of Hsps as a result of oxidative stress secondary to vasoconstriction and metabolic breakdown. The upregulation of Hsps would in turn augment the innate and adaptive immune responses against melanocytes.

NGFs and Their Receptors

Neurotrophins of the NGF family are essential trophic factors secreted by the hypothalamus for the development and maintenance of neurons and other cells derived from neural origin.[143,144] It has been shown that NGF binds to two types of receptors distinguished from each other based on their specificity and affinity for particular neurotrophins: the trkA tyroskine kinase receptor and the p75 NGF receptor.[145,146] The trkA receptor has high affinity and is very specific for certain neurotrophins, whereas the p75 NGFr binds to virtually all members of the NGF family with lower but equal affinity. In general, the effect of NGF

on target tissues depends on the expression level of NGF receptors (both trkA and p75). In the skin, NGF is crucial for the maintenance of sympathetic nerve fibers.[147] This effect is evident in the skin of vitiligo patients, where increased innervations of the aforementioned nerve fibers (NPY, CGRP, p75 NGFr-IR) have been observed. The significant upregulation in the expression of p75 NGFr in vitiligo skin also implies the hyperresponsiveness of the dermal and epidermal environment to NGF in general.

There is increasing evidence that attributes NGF to the role of an important messenger between the nervous system and the immune system. Studies have demonstrated that NGFs are produced by most, if not all, of the major players in the immune system—monocytes/macrophages, neutrophils, granulocytes, and lymphocytes—all of which also express both types of NGF receptors.[148–157] Therefore, NGF is able to influence their proliferation, differentiation, and other functional aspects, such as migration through vascular endothelium during inflammatory responses, in an autocrine and paracrine manner.[147,150,152,155] These activities imply that NGF and receptors have a potential role in the destruction of melanocytes in vitiligo (see Figure 4).

NGF and the corresponding trkA and p75 receptors have been suggested to stimulate the proliferation and differentiation of T and B lymphocytes.[150,155,156] NGF was also suggested to be involved in the development and maintenance of immunologic memory in adaptive immunity.[150,155] Given the suggested hyperresponsiveness of vitiligo skin to NGF and the presence of cytotoxic T lymphocytes and autoantibodies in vitiligo patients against melanocyte-associated markers such as tyrosinase and tyrosinate-related protein,[158–161] it is not unreasonable to assume that the NGF receptors on immune cells of vitiligo patients may also be upregulated and that NGF may play a very important role in the propagation and potentiation of both cell-mediated and humoral response against melanocytes.

Two of the major proinflammatory cytokines that have been observed in vitiligo patients, IFN-γ and TNF-α, could be readily induced by NGF in macrophages, mast cells, and eosinophils, which in turn may produce more NGF along with inflammatory cytokines.[153,162–164] Furthermore, NGF has been implicated in various autoimmune diseases and allergic conditions, such as systemic lupus erythematosus, psoriasis, rheumatoid arthritis, asthma, and urticaria, where serum levels of NGF were significantly increased in patients.[136,139,140] Recently, NGF has been demonstrated to exacerbate inflammation in a mouse model of atopic allergic dermatitis, whereas administration of anti-NGF-neutralizing antibodies substantially alleviated symptoms, including the suppression of TNF-α.[141] As some of these diseases are also associated with vitiligo, it may be worthwhile to further investigate the role of NGF as a mediator in the destruction of melanocytes in the future.

Implications on Therapy

Presently treatment options for vitiligo patients typically involve the direct modulation of immune responses to melanocytes through local immunosuppression with topical corticosteroids, such as clobetasol propionate and betamethasone valerate, and calcineurin inhibitors, such as cyclosporine, pimecrolimus, and tacrolimus,[165,166] which has been shown to stimulate the production of IL-10,[167] an antiinflammatory Th2 cytokine known to counteract excessive immunity in contact dermatitis and Crohn disease.[168,169] Systemic treatment such as oral dexamethasone is also used, albeit with common side effects, including weight gain, acne, and menstrual irregularities in women.[170] Phototherapy such as psoralen in combination with ultraviolet A (PUVA) and narrow-band ultraviolet B (NB-UVB) has also been the mainstream treatment option for vitiligo.

To date, the findings of neural-inflammatory interactions in vitiligo have not been translated into therapeutic advances for patients, whereas neuropeptide receptor antagonists are commonly used in internal medicine (ie, gastroenterology and cardiology). For example, α and β-adrenoreceptor antagonists are used extensively in myocardial infarction and hypertension due to their ability to reverse the effects of catecholamines by acting on adrenergic receptors on endothelial cells. There is also evidence of inflammation suppression by α-adrenoreceptor antagonists, which were shown to downregulate the production of proinflammatory cytokines by lamina propria mononuclear cells and subsequently alleviated acute murine colitis.[171] In addition, α-blockers and β-blockers are also used to treat anxiety and panic disorders by directly inhibiting the release of epinephrine and norepinephrine.[172,173] Therefore, adrenoreceptor antagonists may be potential therapeutic candidates for vitiligo by acting as neuroinflammatory modulators and vasodilators to counter the oxidative stress generated secondary to the vasoconstrictor effect of neuropeptides on endothelial cells. Adrenoreceptor antagonists may potentially complement the immunosuppressants currently prescribed in treating vitiligo, such as topical tacrolimus, which, when used alone, has actually been demonstrated to induce the production and release of neuropeptides in the skin.[174]

Given the association between emotional stress and vitiligo, management and treatment strategies traditionally employed in the field of psychiatry have also demonstrated some success in vitiligo. Antidepressants and antipsychotropic medications were effective in controlling the disease progression when used alone or in conjunction with other treatment options,[175] a finding that has yet to be replicated by others. In addition, there is some preliminary evidence that cognitive behavioral therapy, stress management strategies, and other psychological educational programs have been effective in ameliorating vitiligo severity.[5,176]

Conclusion

Given that neuropeptides and hormones are critical regulators of emotional response and only a small fraction of individuals exposed to mentally stressful situations develop vitiligo, additional factors must be involved in vitiligo pathogenesis. Of major importance is genetic predisposition, as revealed in multiple studies, all of which identified genetic markers that are strongly associated with the development of vitiligo.[177–187] It is worth noting that most of these implicated genetic differences in vitiligo patients are located in genes or chromosomal regions that regulate the innate and, to a lesser extent, adaptive immunity and inflammation, such as *NALP1* and certain major histocompatibility complex alleles. On the other hand, there have been no experimental studies linking these genetic findings with mental stress and neurogenic peptides, although most of the implicated genetic elements have yet to be characterized in terms of their precise physiologic functions. More experimental investigations are warranted to fully understand the role of neurogenic mediators in vitiligo and their potential implications in the development of therapy.

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