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REVIEW

Impact of Psychological Stress-Derived Hormones and Cytokines on Immune Cell Profiles in Vitiligo: Toward Improved Peripheral Blood Simulation in Animal Models

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Abstract: Vitiligo is an autoimmune disease with a localized or generalized depigmentation in the skin, and characterized by psychological stress induced by unattractive appearance. Psychological stress induces alterations in immune cell populations through hormones and cytokines, however, the pathogenesis of psychological stress on vitiligo remains unclear. This review discussed the effects of psychological stress-derived hormones and cytokines including macrophage migration inhibitory factor, progesterone, glucocorticoids, estrogens, and norepinephrine on immunocytes including regulatory T cells, natural killer cells, dendritic cells, B cells, monocytes, and neutrophils. In addition, the review also explored the relationship between melanocytes and immune cells, as well as the conditions of several major animal models simulating the peripheral blood in human vitiligo. This review intended to provide better insights into the complex pathogenesis of vitiligo related to psychological stress, and developing new targets for the prevention and treatments of vitiligo.

Keywords: vitiligo, psychological stress, immunocyte profiles, hormones

Introduction

Vitiligo is an autoimmune skin disease with a chronic depigmentation in the skin, and it affects almost 1% of the global population.[1] The occurrence and progression of many skin diseases and autoimmune disorders are closely linked to psychological stress. Clinical studies have found that individuals with vitiligo are more prone to a variety of mental illnesses compared to the healthy controls. The onset or exacerbation of vitiligo was largely influenced by multiple factors, predominantly psychological stress, leading to common adverse emotions such as anxiety and depression among patients.[2] A pathophysiological link between depression and the development of vitiligo has been found.[3,4] Other reports have focused on the pathophysiology of vitiligo, have made significant progress in demonstrating the interaction between various factors, in particular, the stress hormones and immunocytes and vitiligo, and leading to the formation of depigmentation spots.[5,6]

Vitiligo was accompanied by the changes of Treg cells with pro-inflammatory properties, natural killer (NK) cells, and dendritic cells (DC), as well as activated B cells, monocytes, and neutrophils.[7] Clinical trials found that a reciprocal connection between psychological stress and immune system responses was formed.[8,9] Chronic psychological stress continuously activates the hypothalamic–pituitary–adrenal (HPA) axis: the hypothalamus releases corticotropin-releasing factor (CRF), which stimulates the pituitary gland to release adrenocorticotropic hormone (ACTH); at the same time,

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ACTH induces the expression and release of glucocorticoid, and thereby improves a negative feedback regulation on the hypothalamus.[10] Once the trauma or psychological stress occurs, the glucocorticoid levels were elevated, even glucocorticoid resistance, and accompanied by an increase in the secretion of macrophage migration inhibitory factor (MIF), and maintaining the balance of the immune function. The unique role of MIF in regulating glucocorticoid-mediated immunosuppression placed it at the center of host response.[11,12] MIF is an inflammatory mediator that is associated with the severity of autoimmune diseases, and it may play a key role in the onset and progression of vitiligo, participating in its pathogenesis and serving as an indicator of the disease's severity.[13] MIF is a multifunctional cytokine involved in the stress response of the HPA axis. It modulates macrophage function and can also initiate inflammatory and immune responses by regulating pro-inflammatory cytokines.[14] Additionally, psychological stress activates the sympathetic nervous system, leading to the release of adrenaline and norepinephrine. This neuroendocrine feedback loop is considered crucial in immune-mediated diseases.[15] Furthermore, psychological stress could impact the ability of the production of steroid hormones (adrenocortical hormones and sex hormones), which, in turn, modulated HPA axis activity.[16] Psychological stress induced deceases in the level of sex hormones such as estrogen and progesterone in rodents.[17] Multiple studies highlighted the pivotal role of sex hormones in driving immune responses and regulating autoimmune diseases.[18,] For example, progesterone enhances the crosstalk of macrophage and neutrophil in the cervix, and improves the vaginal neutrophil activation.[19] Chronic stress can cause neuro-immune interaction disorder, which is specifically manifested as the imbalance of NK cell tissue resident homeostasis, the inhibition of T cell and B cell effector function, and the abnormal increase of interleukin (IL)-1β, IL-6, tumor necrosis factor tumor necrosis factor (TNF)-α and other proinflammatory factors, forming a systemic low-grade inflammatory microenvironment.[20] Following chronic stress exposure, mice exhibited significant psychological and physiological alterations, including depression-like behaviors and reduced insulin levels.[21] Early-life stress-induced hypothyroidism by suppressing the expression of orthodenticle homeobox 2 (OTX2), a gene regulated by thyroid hormones. OTX2 served as a critical determinant of midbrain dopaminergic development.[22] Research also demonstrated that chronic stress reduced leptin, a satiety hormone.[23]

In present, vitiligo is involved in autoimmunity, inflammation, and oxidative stress. Less attention has been given to the mechanisms underlying psychological stress, which are summarized in this review. This review highlighted the impact of psychological stress-derived hormones and cytokines on Treg, NK cells, DC, B cells, and neutrophils. The goal is to identify the most suitable cells and hormones for better simulating the peripheral blood environment of human vitiligo using animal models, thereby offering better insights into the complex pathogenesis of vitiligo and developing new clinical treatments for vitiligo.

Functional Impairment of Treg Cells by Psychological Stress-Derived Hormones is Susceptibility to Vitiligo

The functional impairment of Treg cells results in failed suppression of melanocyte-specific cluster of differentiation (CD8)+ T cells, triggering autoimmune attacks. In a mouse model of vitiligo, overexpression of the chemokine ligand (CCL) 22 in the skin increased Treg migration and reduced depigmentation.[24] The C-C chemokine receptor (CCR6)/CCL20 signaling pathway contributes to recruiting skin-infiltrating Treg cells. Interestingly, Chemokine (C-X-C motif) receptor (CXCR) 3 is not necessary for Treg inhibition or migration to the skin, and blocking the chemokine (C-X-C motif) ligand (CXCL) 10/CXCR3 axis does not directly affect Treg suppressive capacity in mediating depigmentation.[25] Therapies targeting CXCL9 or CXCL10 to inhibit Treg migration do not directly impact Treg inhibitory activity.[26] In vitiligo skin, mRNA levels associated with Treg function, such as forkhead box P3 (Foxp3), cytolytic T lymphocyte-associated antigen-4, transforming growth factor (TGF)-β, CCL21 (ligand for chemokine receptor CCR7), and CCL22 (ligand for chemokine receptor CCR4), are reduced.[27] In patients with vitiligo, a decrease in NK cell inhibition was mediated by Tregs, potentially leading to increased destruction of melanocytes.[28] Another study indicated that impaired Treg suppressive function in patients with vitiligo was associated with reduced nuclear factor-activated T cell 1 (NFATC1), FOXP3, CD25, TGF-β, and IL-10, resulting in increased $CD8^+$ and $CD4^+$ T cell numbers and interferon (IFN)-γ production.[29] Furthermore, the reduction of NFATC1 in patients with vitiligo was correlated with decreased FOXP3, thus affecting the regulation of Treg function. Due to decreased production of

immunosuppressive cytokines (IL-10 and TGF-β) and increased production of IFN-γ, perforin, and granzyme B by TRM-based Tregs and antigen-specific Tregs, the impaired and damaged TRM-Tregs cannot inhibit the cytotoxic function and proliferation of $CD4^+$ and $CD8^+$ TRMs, ultimately compromising melanocyte survival.[30]

Anxiety symptoms were correlated with lower percentages of $FoxP3^+$ Treg cells, as well as $Helios^+$ and $TIM\text{-}3^+$ subpopulations.[31] Treg cells play a crucial role in the occurrence and development of autoimmune skin diseases. Peripheral blood Treg cells exhibited pro-inflammatory Th1-like characteristics rather than immunosuppressive properties in the patients with vitiligo.[7] Acute psychological stress reduced $CD4^+FOXP3^+$ T cells and also decreased $CD4^+$ T cells expressing Treg-related effector molecules, such as cytotoxic T lymphocyte antigen-4 and latency-associated peptide.[32] Similarly, chronic stress promoted the suppressive function of $CD4^+CD25^+$ Tregs in the spleen cells of mice.[33]

In addition, corticotropin-releasing hormone (CRH) downregulates the expression of dedicator of cytokinesis 8 in Treg cells and also triggers Treg-mediated inhibition of $CD4^+$ T cells.[34] CRH decrease the proportion of $IL\text{-}10^+$ type 1 regulatory T cells, a subset of Treg, in patients with atopic dermatitis.[35] Furthermore, endogenous catecholamines, including norepinephrine and epinephrine, assisted in the autocrine/paracrine loop involving the dopamine pathway and led to downregulation of Treg function.[36] The beta 1 and 2 adrenergic receptors ($\beta_{1/2}$ AR) – cyclic AMP (cAMP) signaling pathway regulated the molecular switch of T helper 17 cells (Th17)/Treg immune balance that adrenergic signaling promoted the differentiation of Th17 cells but also maintained the pro-inflammatory state by inhibiting Treg polarization.[37] Once the direct target of glucocorticoids, glucocorticoid receptor (GR), was blocked in the Treg cells, hair regeneration was inhibited without affecting immune homeostasis via GR- and Foxp3-induced the upregulation of TGF-β3 in Treg cells, and thereby activating Smad2/3-mediated hair follicle stem cells proliferation and hair regeneration.[38] In the hair pigmentation process, once the stem cell niche was broken by autoimmune attack from dysfunction of Treg cells, the adaptive patterning of the migrated melanocytes within the hair follicle was blocked.[39] Therefore, glucocorticoid-mediated disturbance in Treg cells explain the formation of white hair by psychological stress in the patients with vitiligo. In addition, MIF, as a biomarker of vitiligo, increased Treg production by regulating IL-2, thereby promoting tumor growth.[40] MIF-CD74/CXCR4 signaling pathway increased the number of tumor-infiltrating Treg cells and suppressed the anti-melanoma immune response.[41] During the 12th week of pregnancy, accompanied with an increase in estrogen and progestogen levels, increased perceived stress was associated with a lower percentage of $PD\text{-}1^+$ Treg subpopulations.[31] However, the changes of estrogen and progestogen on vitiligo remained unknown.

NK Cell Regulation of IFN-γ and Cytotoxic T Cells by Psychological Stress-Derived Hormones is Related to Vitiligo Development

Under psychological stress conditions, both NK cells and ILC1 produced IFN-γ, and inducing the production of chemokines that activated T cells, which might be involved in the development of early vitiligo.[42] NK cell receptor NKG 2D was stably expressed in response to various pro-inflammatory type 1 related cytokines and chemokines that were upregulated in the skin of patients with vitiligo.[43] Melanocytes of patients with vitiligo had strong expression of the chemokine receptor subtype 3B (CXCR3B), regulated by IFN-γ. CXCR3B acted as a target for the prevention and treatment of vitiligo, affecting the early steps of melanocyte destruction.[44] NK cell-induced, CXCR3B-mediated apoptosis of melanocytes initiated the auto-reactivity of T cells, which was associated with their involvement in the early development of vitiligo. The NK cell function increased in vitiligo was also related to the destruction of melanocytes.[28] In addition, $CD56^+$ lymphocytes were primarily distributed in the early regression areas in the melanoma, and NK cells might have acted as cytotoxic effector cells in the occurrence of regression.[45]

NK cells, as part of the group 1 innate lymphoid cells (ILC1), serve as the first line of defense against viral infections and malignant cells. When exposed to psychological stress, NK cells produce high levels of IFN-γ, emphasizing their critical role in initiating the autoimmune response.[46] Additionally, NK cells secrete cytokines (eg, CD122, and CD127) and chemokines (eg, CXCR1, CXCR3, and CXCR4) to recruit other immune cells for subsequent adaptive responses.[47] NK cells directly kill oxidatively stressed melanocytes via perforin/granzyme and activate T cells through IFN-γ secretion.[48] Current evidences revealed a spatiotemporal association between psychological stress-induced NK cell functional heterogeneity and norepinephrine fluctuation.[49] Norepinephrine can suppress the cytotoxicity of the NK cell

line, NK92-MI cells, and the expression of perforin, granzyme B, and IFN-γ through the β_2 AR/cAMP/PKA/p-CREB signaling pathway.[50] Norepinephrine pretreatment significantly reduced the binding of $CD16^+$ NK lymphocytes from human peripheral blood mononuclear cells (PBMCs) to K562 cells, a model of erythroleukemia. The treatments of K562 cells downregulated the expression of CD16 (Fc γ RIII) in human PBMCs. These suppressions demonstrated that norepinephrine-mediated induction of NK cells was essential for antibody-dependent cellular cytotoxicity and cytokine production. Norepinephrine also inhibited the upregulation of CD69, an activation marker, mediated by IL-2, while IL-2 critically drove NK cells maturation. At the same time, norepinephrine concentrations in the range of 10^{-6} to 10^{-5} M suppressed TNF-α, IFN-γ, and granulocyte-macrophage (GM)-colony-stimulating factor (CSF) secretion by NK cells, which played critical roles in the maturation and function of IL-2-driven NK cells.[51] In addition, β_2 adrenergic receptor (β_2 AR) agonist inhibited NK cell cytotoxicity in vitro.[52]

On the other hand, glucocorticoids upregulate programmed cell death protein 1 (PD-1) transcription in NK cells in response to IL-12, IL-15, and IL-18, leading to increased PD-1 levels.[53] PD-1 blockade can enhance NK cell-mediated antitumor responses. At the epigenetic level, glucocorticoids reduce the transcription of immune effector gene products required for optimal NK cell function, resulting in decreased NK cell activity.[54] MIF specifically triggered NKT cell chemotaxis via CD74 and CXCR2, leading to IFN-γ production.[55] MIF suppressed antitumor immunity by down-regulating NKG2D on NK and CD8+ T cells.[56] Stress affected males and females differently, with females exhibiting a more immunosuppressed NK cell phenotype.[57] The expression of progesterone receptor (PR) was corresponded to progesterone-induced inhibition of IL-12-mediated IFN-γ secretion. The inhibitory effect on IFN-γ was limited to more mature killer immunoglobulin-like $receptor^+$ peripheral blood NK cells, without affecting IFN-γ secretion by $CD56^+$ peripheral blood NK cells.[58]

DCs Regulation of Cytokines by Psychological Stress-Derived Hormones is Related to Vitiligo Development

DCs are the only specialized antigen-presenting cells and can be classified into plasmacytoid dendritic cells (pDCs) and myeloid dendritic cells (mDCs). The function of mDCs is antigen presentation, and they currently represent the most potent professional antigen-presenting cells in the body. On the other hand, pDCs were capable of producing large amounts of type I IFN.[59] Interestingly, recent research indicated that both mDCs and pDCs are elevated in patients with vitiligo compared to healthy controls.[60] DCs uptake melanocyte antigens and present them via HSP70i, activating CD8+ T cells to break immune tolerance.[61] The regulation of pro-inflammatory and anti-inflammatory DCs in patients with vitiligo might affect cytokine production, leading to melanocyte reduction and depigmentation.[62] Uridine diphosphate glucose derived from melanocytes activates DCs in patients with vitiligo. The DC infiltration process was accompanied by uridine diphosphate-glucose (UDP-G) metabolic reprogramming. UDP-G drove DC immune activation by specifically activating the G protein-coupled receptor P2Y14, a purinergic receptor, via the upregulation of the expression of Cxcl9, Cxcl10, and Il-23 in vitro. However, current evidences fail to demonstrate how melanocytes induce DCs-mediated immune activation.[63] DCs also played a crucial role in driving the activation and differentiation of T cells, leading to adaptive immune responses. Elevated long-term IFN-γ levels have been implicated in the development of autoimmune diseases,[64] with T cells being the primary producers of IFN-γ. Damage-associated molecular patterns were recognized by the endocytic low-density lipoprotein receptor-related protein (LRP1/CD91), which highly expressed in the DCs. The DCs activated self-reactive $CD8^+$ T cells,[65] indicating a probable mechanism of melanocyte destruction induced by the interaction of DCs and $CD8^+$ T cells.

Psychological stress activated the HPA axis, leading to cortisol release from the adrenal glands and inducing neural signaling that resulted in neuropeptide secretion. Cortisol and neuropeptides jointly influenced DCs, promoting Th2 and Th17 responses associated with skin inflammation.[66] An increased cortisol by psychological stress upregulated the expression of the inducible factor TSC22 Domain Family Member 3 (TSC22D3), which blocked DC responsiveness to IFN and activation of IFN-γ^+ T cells.[67] Glucocorticoid-induced leucine zipper (GILZ) played a critical role in mediating the effects of most glucocorticoids in immune cells. GILZ promoted an immature DC phenotype and IL-10 production while limiting IL-12 and IL-23 secretion. Additionally, GILZ regulated antigen capture by DCs, emphasizing its role in

modulating DC function.[68] After the human monocyte-derived DCs were treated with dexamethasone, a semi-mature phenotype characterized by low expression of MHC II[69] and CD86[70] occurred. Dexamethasone downregulated CIITA expression, potentially leading to decreased MHC II gene expression and affecting DC maturation.[71]

In addition, the β_2 AR signaling pathway can inhibit DC migration,[72] possibly related to the immunosuppressive function of β-adrenergic signaling. Activation of β_2 AR in Lipopolysaccharide (LPS)-stimulated DCs did not impact their ability to promote T cell proliferation. However, norepinephrine-mediated β_2 AR activation altered the cytokine profile induced by LPS stimulation, affecting the IL-12/IL-23 ratio and impairing Th1 cell development by inhibiting NF-κB and AP-1. In DCs derived from skin, norepinephrine reduced IL-12 production while increasing IL-10 secretion.[73] Thus, there were still few reports showing that catecholamines-induced DCs in vitiligo.

MIF activation of the Src/PI3K signaling pathway and myosin II complex promoted the migration of DCs, indicating that MIF exhibited chemotactic activity towards DCs. Disrupting the MIF-CD74 signaling pathway reduced monocyte immunosuppressive factors and enhanced DC activation of $CD8^+$ T cells.[14]

Progesterone and estradiol promoted apoptotic cell death in mDCs and increased IL-10 and IL-27 levels. However, only progesterone increased IL-13 production and downregulated IL-23 secretion, thus participating in the regulation of immune responses during pregnancy.[74] Sex hormones failed to suppress the upregulation of surface markers on mature DCs. For instance, estradiol induced pro-inflammatory cytokines, including IL-6, IL-12, and TNF-α, and upregulated CD40, CD86, and MHCII expression.[75] However, the exception was estrogen hCG, which inhibited HLA-DR expression.[76] In addition, progesterone upregulated mRNA expression of PI3K, Akt, mTOR, AMPK, PGC-1α, and PPAR-γ in DCs. These signaling pathways may have mediated immune metabolic effects in pDCs.[77] Furthermore, physiological levels of estradiol reduced the efficiency of IL-23 production in DCs.[78,79] However, estradiol at physiological levels promoted IL-1β production in mouse vaginal $CD11c^+$ DCs.[80] Estradiol's impact on DC function varies depending on the concentration and type of DC. Estradiol inhibits the production of α-defensin 1–3, an important regulatory molecule in the immune system and whose level is a highly sensitive method to reveal the presence of inflammatory processes, in mDCs and monocyte-derived DCs, while pDCs remained unaffected.[81] Testosterone (androgen) had immunosuppressive effects on DCs, reducing the production of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α.[82] A direct link between psychological stress, sex hormone fluctuation, and DC function remains to be verified.

B Cell Regulation of Humoral Immunity and Autoantibody Production by Psychological Stress-Derived Hormones

The onset of vitiligo might be related to the following mechanisms: autoreactive B cells were activated, producing autoantibodies against melanocytes; B cells acted as adjuvants, enhancing $CD4^+$ T cells' activation of $CD8^+$ T cells in response to melanocyte antigens, leading to autoreactive responses; activated B cells captured antigens and presented them directly to $CD8^+$ T cells.[83] Immune cell infiltration in vitiligo was related to the expression of antigen-presenting related genes, observing a positive correlation between the expression of dynactin Subunit 5 (DCTN 5) and endoplasmic reticulum aminopeptidase 2(ERAP 2) and the abundance of B cells.[84]

The chronic stress mouse model exhibited abnormal humoral immune function, characterized by impaired plasma cell differentiation and diminished antigen-specific antibody production. Notably, unimmunized stressed mice displayed dysregulated B-cell homeostasis, marked by aberrant expansion of age-associated B cells and spontaneous autoantibody production, accompanied by aggravated autoimmune manifestations. Transcriptomic profiling identified downregulated expression of genes associated with B cell-mediated immune responses and upregulated pathways linked to autoimmune activation in this model.[85] After antigen activation, norepinephrine and glucocorticoids regulated macrophages and T cells to produce cytokines, promoting humoral immunity.[86] Glucocorticoids could induce apoptosis in autoreactive B cells by lowering B cell activator factor levels.[87] The upregulation of CXCR4 expression in B cells by glucocorticoid may partially explain the reduction in B lymphocytes associated with infection, inflammation, and physical stress.[88] Cortisol increased miR-98 expression in B cells. Cortisol also inhibited IL-10 expression in B cells, where miR-98 played a crucial role.[89] The intrinsic GR signaling pathway in B cells can directly enhance IgE production by glucocorticoid even in the absence of antigen attack. This pathway strengthened the CD40 signaling pathway and synergized with the

IL-4/STAT6 pathway.[90] B cell-mediated humoral immunity is thought to involve the immune response to vitiligo,[7] indicating that the changes of B cells in vitiligo might be related to stress hormones of catecholamines and glucocorticoids. In addition, MIF initiated a signaling cascade involving Syk and Akt, leading to NF-κB activation, proliferation, and survival in a CD74- and CD44-dependent manner in B lymphocytes, thereby regulating adaptive immune responses.[91] However, there are few data supporting psychological stress-derived sex hormones on B cells.

Monocytes Regulation of Pro-Inflammatory Factors by Psychological Stress-Derived Hormones is Related to Vitiligo Development

Monocytes differentiate into macrophages releasing TNF-α/ROS, which amplifies oxidative stress and establishes a pro-inflammatory-damage cycle. Monocytes were involved in the development of vitiligo, but their function remained unclear.[42] In patients with vitiligo, monocytes exhibited an upregulation of genes related to inflammatory proteins such as TNF, CCL3, and NLRP3.[7] Acute stress-driven cortisol induced the expression of CXCL12 in skin melanocytes, and promoted the migration and redistribution of CXCR4α-positive macrophages activated by stress in the skin.[92] Consequently, monocytes in the patients with vitiligo displayed a pro-inflammatory phenotype, and promoting an inflammatory state through the release of pro-inflammatory cytokines and chemokines.

In LPS-stimulated monocytes from stressed mice, the expression of genes in the PI3K and mTOR signaling pathways was upregulated, which was associated with the upregulation of genes related to myeloid immune responses. This suggested that psychological stress-induced inflammation in the body resulted from the reprogramming of bone marrow cells, including monocytes, providing an explanation for how psychological stress can lead to inflammatory diseases.[93] IL-6 was a key factor in activating peripheral monocytes, which were recruited and trigger anxiety-like behavior during stress. The lack of IL-6 was associated with an overall reduction in inflammatory signals and a lack of anxiety-like behavior, resulting in monocytes exhibiting diminished inflammatory features, including reduced expression of IL-1β.[94]

The effects of β-adrenergic receptors on monocytes primarily demonstrated immunosuppressive and anti-inflammatory properties, such as the downregulation of TNF-α expression, reduced phagocytosis of Candida albicans, and inhibition of IL-18 and IL-12 production in LPS-treated monocytes.[73] Psychological stress inhibited the anti-inflammatory effect of PD-L2-positive macrophages dependent on the β2 AR and led to the accumulation of necrotic cells, thereby upregulating CCL24-mediated eosinophil infiltration in IgE-mediated cutaneous allergic inflammation.[95] In addition, corticosteroids reduced IL-12 production in monocytes, leading to decreased ability to induce IFN-γ and increased IL-4 capacity in T cells.[96] While glucocorticoids inhibited monocyte activation by LPS, they also induced an anti-inflammatory monocyte phenotype, resulting in the production of anti-inflammatory mediators to prevent cell apoptosis. Glucocorticoids enhanced migration and phagocytic abilities.[97] Cortisol upregulated the expression of the chemokine receptor CCR2 in $CD14^{+}$ monocytes and migration activity toward CCL2 (MCP-1).[98] MIF overcame the inhibitory effect of glucocorticoids on LPS-induced production of TNFα, IL-1β, IL-6, and IL-8 in monocytes in vitro.[99]

Under the influence of estrogen, the primary estrogen receptor in PBMCs was ERα. Additionally, ERβ2 mRNA was more abundant than ERβ1 in PBMCs, suggesting that ERβ2 might have played previously unexpected roles in immune responses. Furthermore, Peik found that the expression of several relevant immune genes in PBMCs fluctuated during different phases of the menstrual cycle (when estrogen and progesterone were released). These genes included those encoding pro-inflammatory responses (IFNG, TNFA, and IL-1B) and Th1- and Th2-related genes (GATA 3 and TBX 21).[100] Progesterone increased TNF-α production in corpora lutea macrophages, and promoted the expression of CXCL2 in monocyte-derived macrophages, thereby improving the crosstalk of macrophage-neutrophils.[19,101] Estradiol downregulated the expression of secretory leukocyte protease inhibitor (SLPI) in monocytes. SLPI is an anti-protease with immunomodulatory effects. Additionally, estradiol upregulated the expression of miR-19, which occurred through increased activity of the c-MYC-mediated MIR 17 HG promoter. This demonstrated that estradiol could reduce SLPI expression in monocytes by regulating miRNA expression, emphasizing the potential role of estrogen in immune responses.[102] These findings contributed to a better understanding of the interplay between sex hormones and immune reactions. Progesterone could downregulate CD80 expression on mature bone marrow-derived dendritic cells (BMDCs), but only at its highest concentration. Progesterone directly inhibited mature rat BMDC-driven pro-

inflammatory responses, potentially explaining a difference in vitiligo between women and men.[103] Thus, the findings above were benefit to investigate the mechanism of psychological stress-mediated hormones and cytokines on macrophages in vitiligo.

Neutrophils Regulation of Other Immunocytes and Oxidative Stress by Psychological Stress-Derived Hormones is Related to Vitiligo Development

Neutrophils are the most abundant type of granulocytes and belonged to the polymorphonuclear leukocyte family, and act as the first responders to infections or inflammation.[104] Neutrophils released neutrophil extracellular traps (NETs), which not only killed invading pathogens but also served as a source of self-antigens. Almost all immune cells during inflammatory responses made a crosstalk with neutrophils.[105] In mechanism, neutrophils release autoantigens via NETs, and directly damaging melanocytes via activating immune responses. The CSF3R could regulate the survival, proliferation, and differentiation of neutrophils, and CSF3R was located in the cytoplasm and cell membrane of melanocytes and neutrophils.[106]

Chronic psychological stress promoted neutrophil infiltration through β-adrenergic signaling.[107] Epinephrine down-regulated the pro-inflammatory activity of neutrophils by enhancing cytoplasmic Ca^{2+} clearance through cAMP.[108] Treatment with norepinephrine significantly impaired neutrophil chemotaxis after 4 hours and induced an N2 neutrophil phenotype, resulting in decreased expression of key genes related to cellular inflammation. Prolonged norepinephrine treatment promoted the release of myeloperoxidase and IL-6 from neutrophils but inhibited the production of IFN-γ and IL-10, and leading to a decreased neutrophil activation and phagocytic activity.[109] However, the ratio of neutrophils to lymphocyte was decreased in patients with vitiligo.[110] Whether the increment of neutrophils by psychological stress is less than that of lymphocyte remain unclear. As a key mediator of stress-induced behavioral disorders, CD177 on neutrophils could be upregulated by psychological stress.[111] The genes CCR1 and CXCR2 (primarily expressed in neutrophils) and CCR2 (primarily expressed in monocytes) were upregulated by acute stress.[112] The transient increase in neutrophils and monocytes induced by norepinephrine was similar to the effects of psychological stress.[113]

GR activated by glucocorticoids might regulate the homeostasis of circulating neutrophils by negatively affecting Fas gene expression and downstream apoptotic signaling pathways.[114] GILZ was specifically expressed in human neutrophils and mediated the bidirectional immunomodulatory effects of glucocorticoids on anti-infective functions through down-regulating Toll-like receptor 2 (TLR2) while suppressing excessive inflammatory responses, this mechanism concurrently compromised critical pathogen-clearing immune capacities.[115] MIF and its homolog MIF-2/D-DT inhibited neutrophil

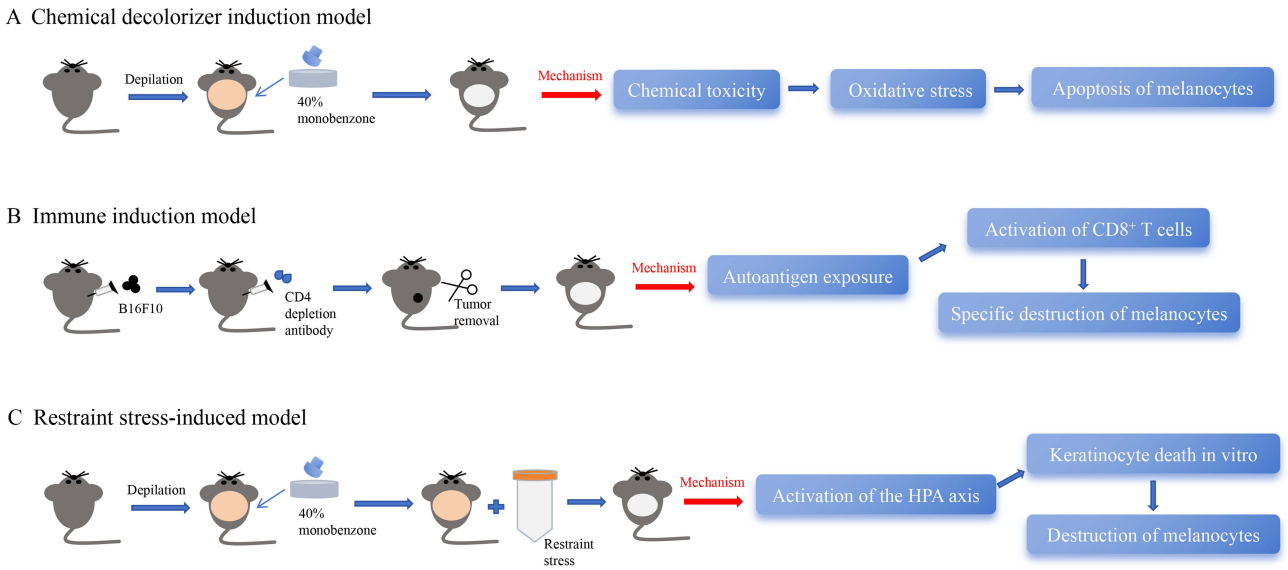

Figure 1 The development of vitiligo-like mice models. (**A**) Apply 40% monobenzone to the skin of mice to induce oxidative stress, resulting in hair pigment loss in mice. (**B**) Inoculate mice with B16F10 melanoma cells, then inject anti-CD4 antibodies to deplete Treg cells, and finally surgically resect the primary tumor to induce the occurrence of vitiligo in mice. (**C**) Use 40% monobenzone application combined with chronic restraint stress to simulate the impact of psychological stress on pigment loss.

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apoptosis, resulting in the release of CXCL8, IL-6, and potentially G-CSF and GM-CSF.[116] Estradiol inhibited the production of IL-1β by neutrophils and macrophages, thereby regulating the production of IL-17 A by T cells.[117]

Common Vitiligo Animal Models

Recently, few animal models with vitiligo-like changes had been applied. Vitiligo models can be induced by some skin depigmenting agents including monobenzone, hydrogen peroxide, and hydroquinone, etc.[118,119] The skin depigmentation in the afore-mentioned models was mainly caused by chemical stress leading to melanocyte loss, which did not fully reflect the pathological characteristics of autoreactive $CD8^+$T cell-induced melanocyte loss in the patients with vitiligo. Thus, to translate these mechanistic insights into therapeutic advances, robust animal models that accurately mimic the human condition are essential. Based on the monobenzone-induced mouse mode,[120] our previous reports established a vitiligo-like mouse model induced by restraint stress combined with monobenzone, and simulating an increased peripheral blood $CD8^+$ T cell level in environment of vitiligo.[121] Furthermore, other transgenic vitiligo mouse models were established by transferring melanocyte-specific $CD8^+$ T cells into mice with retain melanocytes in the skin.[122] An immune-induced vitiligo mouse model induced by B16 F10 and anti-CD4 antibodies was established, and commendably simulating the pathogenesis of human with vitiligo[123,124] (Figure 1). In addition, regional IFNγ-resistant fibroblasts determine the depigmentation of skin in vitiligo-like mice,[125] however, there were few reports explored psychological stress-derived hormones on fibroblasts with IFNγ-secreted immune cells.

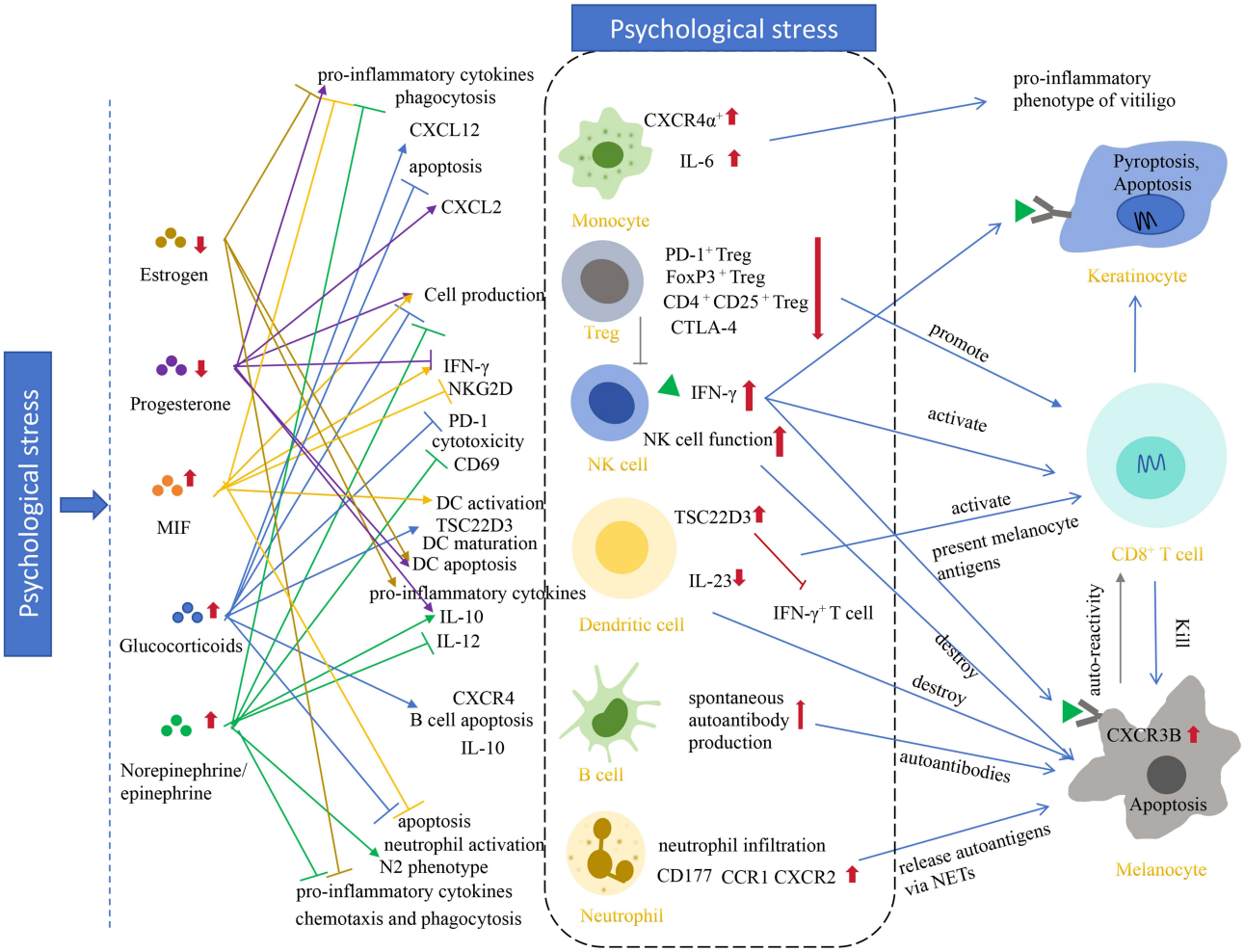

Figure 2 A schematic graph demonstrates the effect of psychological stress-derived hormones and cytokines on immunocyte profiles in vitiligo. Psychological stress-derived hormones and cytokines triggered six immune cells including Treg, NK cells, DC, B cells, and neutrophils from peripheral blood to influence keratinocytes, $CD8^+$ T cells, and melanocytes in the microenvironment of skin of human vitiligo.

Conclusions

The review summarized the impact of psychological stress-derived hormones and cytokines on immune cell profiles in vitiligo, and introduce the animal models of vitiligo toward improved peripheral blood simulation. Psychological stress increased the levels of adrenaline, norepinephrine, glucocorticoids, and MIF, and induced decreased levels of estrogens and progesterone. These hormones and cytokines can target Treg, NK, DC, B cells, monocytes, and neutrophils, and simulate the changes of peripheral blood environment in humans, particularly in the patients with vitiligo (Figure 2). Psychological stress-derived hormones, such as norepinephrine, glucocorticoid, and sex hormones, can have serious effects on human health and are closely related to immune-mediated diseases. These hormones can influence immune cells and induce autoimmune diseases like vitiligo. Progesterone directly affects the expression of many immune-related genes, which can influence the activity and function of immune cells, thereby increasing the risk of autoimmune diseases in women. For example, changes in female hormone levels during menstruation and pregnancy may lead to abnormal activation of the immune system, and thus triggering an autoimmune response.

According to this review, methods that administer MIF or anti-progesterone on the basis of monobenzone may induce the development of vitiligo, and in animal experiments, may simulate the development of vitiligo patches and the peripheral blood environment of human vitiligo, in hopes of providing better insights into the complex pathogenesis of vitiligo and developing new clinical treatments for vitiligo.

Data Sharing Statement

The data used to support the findings of this study are available from the corresponding authors upon request.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that there is no conflict of interest regarding the publication of this article.

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