# Roles of inflammation factors in melanogenesis (Review)

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**Abstract.** The occurrence of hyperpigmentation or hypopigmentation after inflammation is a common condition in dermatology and cosmetology. Since the exact mechanism of its occurrence is not yet known, prevention and treatment are troublesome. Previous studies have confirmed that α-melanocyte-stimulating hormone, stem cell factor and other factors can promote melanogenesis-related gene expression through the activation of signaling pathways. Recent studies have revealed that a variety of inflammatory mediators can also participate in the regulation of melanogenesis in melanocytes. In this review, we summarized that interleukin-18, interleukin-33, granulocyte-macrophage colony stimulating factor, interferon-γ, prostaglandin E2 have the effect of promoting melanogenesis, while interleukin-1, interleukin-4, interleukin-6, interleukin-17 and tumor necrosis factor can inhibit melanogenesis. Further studies have found that these inflammatory factors may activate or inhibit melanogenesis-related signaling pathways (such as protein kinase A and mitogen activated protein kinase) by binding to corresponding receptors, thereby promoting or inhibiting the expression of melanogenesis-related genes and regulating skin pigmentation processes. This suggests that the development of drugs or treatment methods from the perspective of regulating inflammation can provide new ideas and new targets for the treatment of pigmented dermatosis. This review outlines the current understanding of the inflammation factors' roles in melanogenesis.

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**Contents**



## 1. Introduction

A coordination system has been formed under the interaction of various cells in the skin. For instance, the cutaneous neuron-immune-endocrine system consists of interaction and coordination between keratinocytes, melanocytes and dendritic Langerhans cells in the epidermis and the components of the dermis such as mast cells, macrophages, fibroblasts and nerve cells (1-3). Allergens, pathogens, chemical stimuli, and physical damage can all lead to skin inflammation (4-7), which is a defense response to exogenous or endogenous stimuli (8). Skin inflammation plays a crucial role in the body, such as resisting the invasion of bacteria and other pathogens and promoting the repair of wounds. Recent studies have revealed that inflammatory cytokines are closely related to skin pigmentation (9,10).

Skin hyperpigmentation or hypopigmentation after inflammation is a clinically common symptom. Various acute or chronic inflammatory skin reactions may cause changes in skin pigmentation (11), such as psoriasis, eczema, or laser surgery. Recent studies have confirmed that interleukin (IL)-1, IL-4, IL-6 and other inflammatory mediators can regulate the proliferation and differentiation of human epidermal melanocytes directly or indirectly and participate in the regulation of melanogenesis in melanocytes (11-13). Treatments that modulate these inflammatory mediators may have great clinical utility in the treatment of some dyschromatosis (14). This review will focus on the role of inflammatory factors in melanogenesis and the mechanisms involved.

## 2. Process of melanogenesis

Melanocytes originate from the ectodermal neural crest, migrate to the mesenchyme as the embryo develops, and

then further migrate to the skin, eye uveal, stria vascularis, vestibular organ, endolymphatic sac and pia mater (15,16). The migration, proliferation, and differentiation of melanoblasts are mainly regulated by regulatory factors secreted by the dorsal neural tube, ectoderm, and keratinocytes such as the fmily of Wingless-type protein (WNT), endothelin 3 (EDN3), and stem cell factor (SCF) (17). Melanogenesis in mature melanocytes occurs in melanosomes. Melanosomes are unique organelles located in the cytoplasm of melanocytes, which contain key enzymes regulating the production of pigments such as tyrosinase (TYR), tyrosinase-related protein-1 (TYRP-1) and tyrosinase-related protein-2 (TYRP-2) (17,18). Activation of the transcription factor microphthalmia-associated transcription factor (MITF) (19-21) results in the upregulation of the expression of key genes such as TYR, TYRP-1 and TYRP-2 (16,22,23), and promotes melanogenesis in melanocytes (17). Mature melanosomes can migrate from the perinuclear region to the dendrites of melanocyte under the regulation of tubulin (kinesin, dynein) (17). In the epidermis, melanocytes are associated with 30 to 40 keratinocytes through dendrites, transferring mature melanosomes into the cytoplasm of keratinocytes (15,24).

## 3. Signaling pathways regulating melanogenesis

Multiple signaling pathways are involved in the regulation of melanogenesis, with the cyclic AMP (cAMP)/protein kinase A (PKA) signaling pathway being one of the most important signaling pathways (Fig. 1). The most well-known receptor on melanocytes that modulates their function is the melanocortin-1 receptor (MC1R). When α-melanocyte-stimulating hormone (α-MSH) binds to MC1-R on the membrane of melanocytes, it activates adenylate cyclase, increases intracellular cAMP, activates PKA-cAMP response element-binding protein (CREB) pathway, and then increases MITF, promoting melanogenesis (25-28). MC1R is also a major regulator of human pigmentation and is also a melanoma susceptibility gene (28). In addition, signaling pathways such as mitogen activated protein kinase (MAPK), inositol trisphosphate/diacylglycerol (IP3/DAG), WNT, and protein kinase C (PKC) have also been revealed to participate in melanogenesis. The α1 adrenergic receptor can activate the IP3/DAG pathway and increase the intracellular levels of PKC-β and activate tyrosinase (29). SCF, GM-SCF and hepatocyte growth factor (HGF) can activate signaling pathways mediated by the corresponding receptor c-KIT, GM-CSFR, and HGFR, leading to autophosphorylation and activation of MAP kinase, thereby phosphorylating MITF, upregulating the expression of melanogenesis-related enzymes (30-32). The WNT signaling pathway can activate MITF-M promoter (33-35), thereby resulting in upregulation of MITF expression to further regulate melanogenesis. Catecholamines can promote melanogenesis through the cAMP/PKA pathway, while catecholamines also mediate melanogenesis through the activation of PKC-β pathways by α1 and β2 adrenergic receptors (29,36).

Skin melanogenesis is affected by the epidermal melanin unit, which is mainly composed of keratinocytes and melanocytes. Many of the paracrine factors secreted by keratinocytes can act on melanocytes to promote or inhibit melanogenesis. For example, IL-18, IL-33, GM-CSF can promote melanogenesis, and TNF, IL-1 and IL-6 can inhibit melanogenesis (37,38). In addition to keratinocytes, other types of cells in the skin, such as fibroblasts, also participate in the regulation of melanocytes by producing paracrine factors (Fig. 2). Melanocytes interact with these surrounding cells by expressing corresponding receptors on the cell surface (27). In addition, studies have revealed that paracrine factors can provide a variety of mechanisms to activate DNA repair mechanisms by activating different receptors and signaling pathways to maintain melanocyte homeostasis and prevent UV mutagenesis (28).

## 4. Function and mechanism of inflammatory factors in regulating melanogenesis

Inflammation is a basic pathological process mainly involving defensive reactions of living tissues with a vascular system in response to the stimulation of various damage factors. The chemical factors involved in mediating inflammatory reactions are called chemical mediators or inflammatory mediators. The inflammatory mediators in the skin are mainly secreted by Th cells, lymphocytes, monocytes-macrophages, dendritic cells, and the like. Th cells are mainly classified as Th1 and Th2 cells (39). Th1 cells play an important role in cellular immune responses, secreting cytokines such as interferon-γ (IFN-γ), tumor necrosis factor (TNF), IL-2, IL-3, GM-CSF; Th2 cells play a key part in humoral immune responses, secreting IL-4, IL-5, IL-10, IL-13, IL-3, GM-CSF as well as other cytokines (40,41). In a normal body, Th1 cytokines and Th2 cytokines are in equilibrium. When the body suffers from a certain disease, the balance between Th1 and Th2 is impaired, and there is a drift toward Th1 or Th2 (39). T helper cell 17 (Th17) is a newly discovered T cell subset that secretes IL-17, IL-6, IL-21 and IL-22 and participates in the occurrence of innate immunity and certain inflammations by secreting IL-17, IL-6 and TNF-α. Studies have revealed that keratinocytes can secrete IL-18, TNF, IL-1, GM-CSF, INF-γ, and IL-3, fibroblasts can secrete IL-33, TNF, IL-6, and IL-8, and melanocytes can secrete INF-β, IL-1, IL-8, IL-10 and TNF-α (37,38,42). The main inflammatory mediators that are secreted by various types of cells in the skin are presented in Table I. Recent studies have revealed that local inflammatory factors of the skin may be involved in the regulation of skin pigmentation (Fig. 3). The function and mechanisms of these inflammatory factors in regulating melanogenesis are presented in Table II.

IL-18 is produced by inflammatory stimuli in Langerhans cells (LC), dendritic cells (DC), Kupffer cells, activated monocytes/macrophages, and keratinocytes in the epidermis (43-45). IL-18 has been revealed to increase the cascade expression of MITF and downstream enzymes by activating the p38/MAPK and PKA pathways, and thus promote melanogenesis and upregulate TYRP-1 and TYRP-2 expression (43,46). These results suggest that IL-18 may participate in the regulation of pigmentation by regulating melanocytes.

IL-33 can induce mast cells to produce pro-inflammatory cytokines and chemokines (47-51), thereby activating macrophages (52-54), $CD4^+$T cells, basophils, dendritic cells and neutrophils (47,55-58), and promoting skin inflammation. It has been revealed that IL-33 mRNA is expressed in multiple organs in humans (including the skin), and in particular, relatively abundant IL-33 mRNA is found in keratinocytes

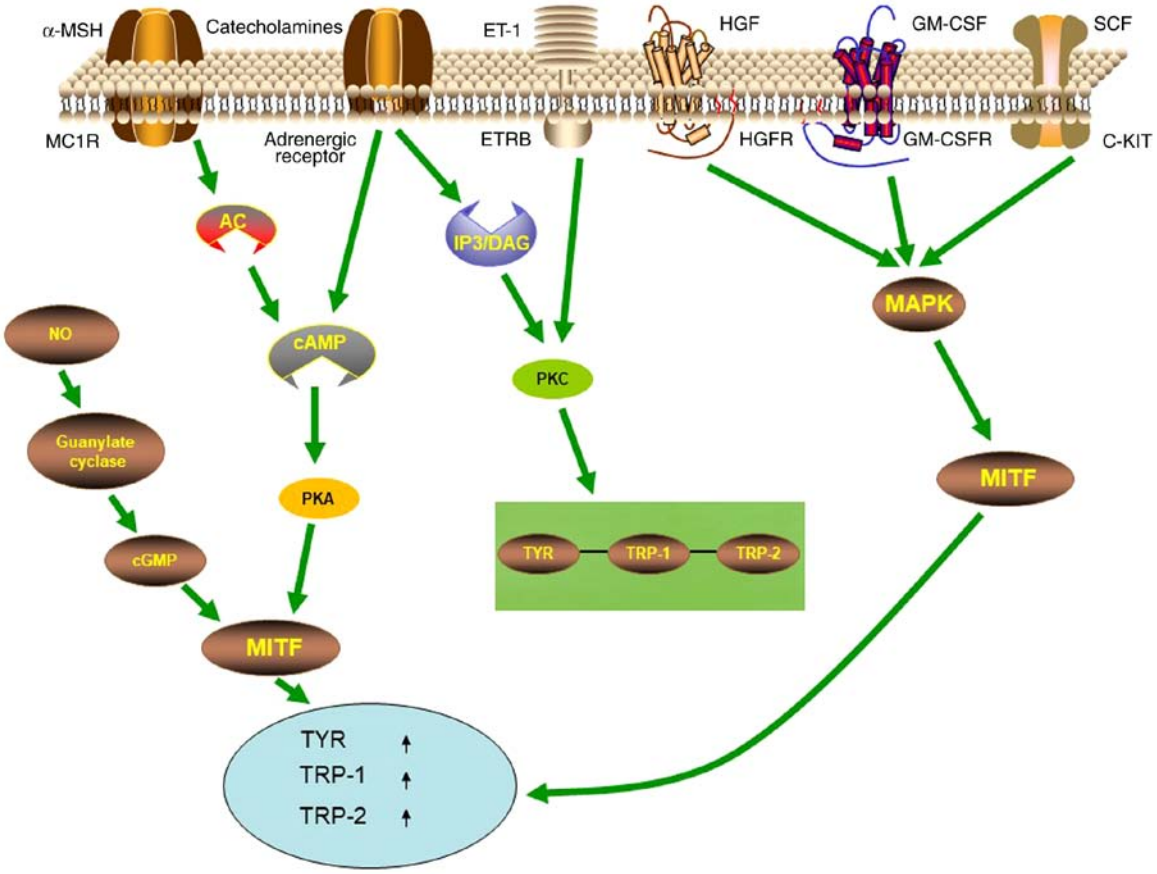


Figure 1. Different signaling pathways regulating melanogenesis. Upon binding to MCIR and adrenergic receptor respectively, α-MSH and catecholamines activate the PKA pathway by increasing cAMP. Then PKA promotes MITF expression, which controls the expression of melanogenesis-related genes TYR, TRP-1 and TRP-2. Upon binding to ETR and adrenergic receptor respectively, ET-1 and catecholamines activate the PKC pathway to promote the expression of TYR, TRP-1 and TRP-2. Upon binding to c-MET, GM-CSFR, and c-KIT and respectively, HGF, GM-CSF, and SCF activate the MAPK pathway to promote the expression of MITF, which in turn increases the expression of TYR, TRP-1 and TRP-2. In addition, NO in the cytoplasm regulates MITF-driven expression of TYR, TRP-1 and TRP-2 through the guanylate cyclase-cGMP pathway. α-MSH, α-melanocyte-stimulating hormone; MC1R, melanocortin-1 receptor; ET-1, endothelin-1; ETR, ET-receptor; HGF, hepatocyte growth factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; GM-CSFR, granulocyte macrophage colony-stimulating factor receptor; SCF, stem cell factor; AC, adenylate cyclase; cAMP, 3'5'-cyclic adenosine monophosphate; PKA, protein kinase A; c-GMP, cyclic guanosine monophosphate; IP3/DAG, inositol trisphosphate/diacylglycerol; PKC, protein kinase C; MAPK, mitogen activated protein kinase; TYR, tyrosinase; TRP-1, tyrosinase-related protein-1; TRP-2, tyrosinase-related protein-2.

and fibroblasts (59,60). Research has revealed that IL-33 can improve melanin biosynthesis in NHEM and promote the expression of MITF and its downstream-regulated tyrosine, TYRP-1, and TYRP-2 through the activation of MAPK and PKA pathways (14), thereby promoting melanogenesis.

In addition, granulocyte-macrophage colony-stimulating factor (GM-CSF) which is produced by mononuclear macrophages, keratinocytes and Th cells, has been revealed to promote melanocyte proliferation and melanin synthesis (17). Wu *et al* revealed that increased serum levels of GM-CSF may be used as the serum biomarkers to predict the prognosis of TCAM (transplantation of cultured autologous melanocytes) when vitiligo patients are treated (61).

Prostaglandin E2 (PGE2) and PGF2α which are produced by fibroblasts and keratinocytes have been revealed to stimulate dendritic cell formation and activate tyrosinase in melanocytes through their dependence on the cAMP signaling pathway and phospholipase C (PLC) (62,63). Ma *et al* revealed that PGE2 is important in melanosome transfer by promoting filopodia delivery (including miniaturization of melanosome, filopodia formation, and broadening diameter of filopodia) and the number of shedding spheroid granules in primary melanocytes (MCs), but has no effects on morphological observation of KCs (64).

As one of the most important endogenous mediators of immunity and inflammation, IFN-γ is also a common secretory cytokine in the skin (46). As a pro-inflammatory cytokine, IFN-γ is mainly secreted by Th1 lymphocytes, $CD8^+$ cytotoxic T lymphocytes and NK cells (65). Other cells, including antigen-presenting cells, B cells and NKT cells, can also secrete IFN-γ (66-68). Recent studies have demonstrated that the local accumulation of IFN-γ through melanocyte-specific $CD8^+$ T cells plays an important role in skin discoloration spots in various mouse models of vitiligo (69,70). Yang *et al* reported that increased IFN-γ is essential for the pathogenesis of vitiligo by inducing apoptosis of melanocytes (71). Natarajan *et al* revealed that IFN-γ signaling blocks maturation of melanosomes by regulating pigmentation genes (72). Moreover, IFN-γ has been revealed to regulate melanogenesis by upregulating STAT1 phosphorylation, and its inhibiting effect can be restrained by JAK1 inhibitors. Studies have also revealed that IFN-γ inhibits IL-18-induced melanogenesis (46).

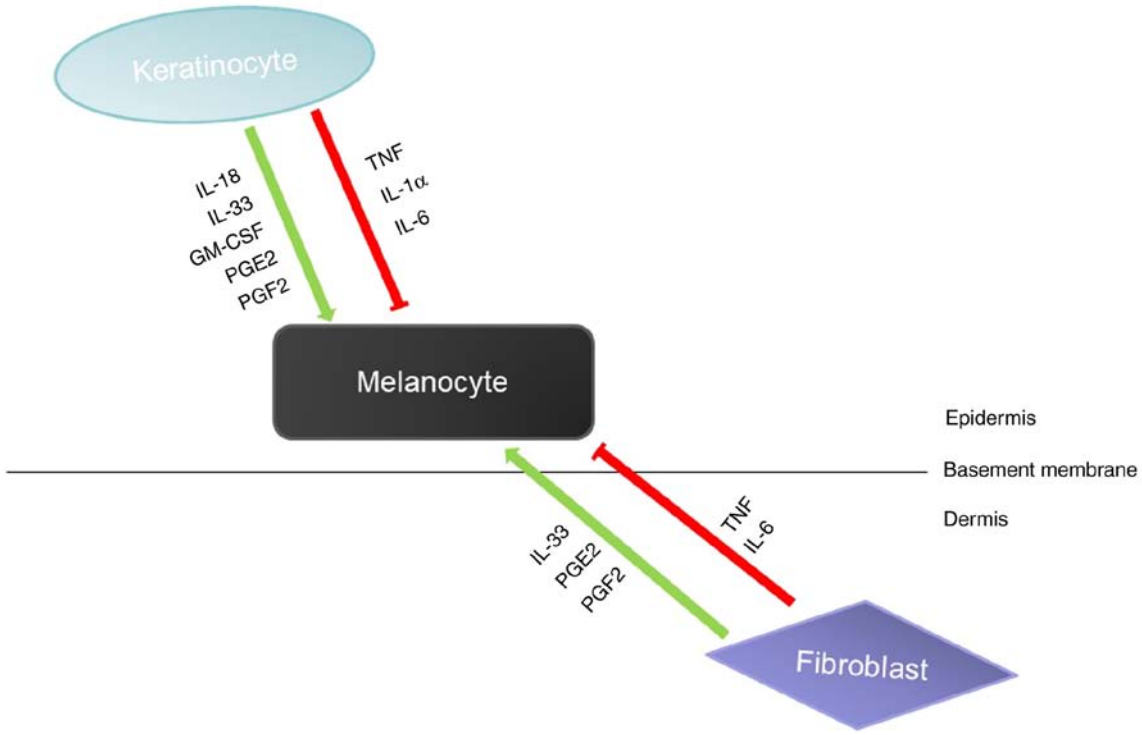


Figure 2. Keratinocyte-derived factors and fibroblast-derived factors that affect melanogenesis in melanocytes through a paracrine effect. Various factors are identified to stimulate (green arrows) or inhibit (red arrows) melanogenesis in melanocytes. Keratinocytes secret factors such as IL-18, IL-33, GM-CSF, PGE2 and PGF2 to stimulate melanocyte melanogenesis as well as TNF, IL-1α and IL-6 to inhibit melanocyte melanogenesis. Fibroblast-derived factors such as IL-33, PGE2 and PGF2 stimulate melanocyte melanogenesis while TNF and IL-6 inhibit melanocyte melanogenesis. IL-18, interleukin-18; IL-33, interleukin-33; GM-CSF, granulocyte-macrophage colony stimulating factor; PGE2, prostaglandin E2; PGF2, prostaglandin F2; TNF, tumor necrosis factor; IL-1α, interleukin-1α; IL-6, interleukin-6.

TNF is a homotrimeric cytokine, secreted mainly by monocytes and macrophages, and also by keratinocytes, dendritic cells, Th1, Th17 and Th22. It functions by binding to two different receptors: TNFR1/p55 and TNFR2/p75 (9). TNF not only induces inflammation through the activation of vascular endothelial cells and immune cells, but also acts as an important regulator of lymphoid tissue development by controlling apoptosis (9). Elevated levels of TNF have been revealed at sites of inflammation in several autoimmune diseases, and inflammatory symptoms have generally decreased after neutralization of TNF. For instance, higher expression levels of TNF, TNFR1 and TNFR2 are observed in psoriasis (73). Studies have revealed that after treatment of melanocytes with both IL-17 and TNF for 24-48 h, the levels of c-KIT, MC1-R, MITF, and TYRP-2 were on the decrease, and the levels of tyrosinase and melanin were significantly reduced (10). It has been revealed that, through the combination with IL-17, TNF can inhibit melanogenesis by PKA and MAPK signaling pathways (9,10). Blocking TNF can lead to rapid restoration of pigmentation gene expression in psoriatic lesions. This suggests that anti-TNF has the potential of treating pigmented dermatosis (10).

IL-1 is an important pro-inflammatory cytokine in innate immunity that stimulates the differentiation and function of immune surveillance cells and contributes to increased tumor invasiveness, metastasis, and angiogenesis under chronic inflammatory conditions (74). IL-1α is an inflammatory mediator mainly produced by Langerhans cells, and is also secreted by melanocytes and keratinocytes. Its signal transduction is initiated by binding to IL-1 receptor type I (IL-1Rα chain) (75), which can inhibit tyrosinase activity and melanogenesis (12,74). Of its many activities, IL-1α also stimulates human fibroblasts to produce keratinocyte growth factor (KGF) (76). Keratinocytes store a large amount of active IL-1α, express IL-1 receptors (77) and produce more IL-1α upon ultraviolet B (UVB) exposure (78). KGF is thought to induce TYR expression in primary melanocytes (79). The combination of KGF and IL-1α increases melanin deposition and they may be involved in the initial stage of human Solar lentigines lesion formation (79). Although they share only 24% identity in protein sequence, IL-1β and IL-1α fold in a highly similar manner and recognize the same receptor, the type I IL-1 receptor (IL-1RI) (80). After treatment of a panel of melanoma cell lines with IL-1β, it was observed that most of the MITF-M was inhibited and was NF-κB- and JNK-dependent. The inactivation of these two pathways could eliminate the inhibitory effects of IL-1β on melanin, which indicated that IL-1β could downregulate MITF-M through NF-kB and JNK pathways, thereby inhibiting melanogenesis (74).

IL-4 is a cytokine mainly secreted by Th2 cells and can also be produced by CD8-positive cytotoxic T cells, basophils, eosinophils, and mast cells in chronic inflammation (81,82). IL-4 plays a key role in the generation of the major mediator IgE in hypersensitivity as well as in the induction of inflammation, contributing to the autoimmunity of the body (83). IL-4 is involved in the maintenance of Th2 lymphocytes and acts as an autocrine growth factor of differentiated Th2 cells (84). It is hypothesized that vitiligo

Table I. Inflammatory mediators secreted by various types of cells in the skin.

| Cell type | Inflammatory factors |
|---|---|
| Mononuclear macrophages | INF-γ, TNF, IL-1, GM-CSF, IL-6, IL-8, IL-12, IL-18, IL-10 |
| Neutrophils | IL-1β, TNF, IL-6, IL-8, IL-15, IFN-γ |
| Th1 cells | IFN-γ, TNF, IL-2, IL-3, GM-CSF |
| Th2 cells | IL-4, IL-5, IL-6, IL-10, IL-13, IL-3, GM-CSF |
| Th17 cells | IL-17, IL-6, IL-21, IL-22, TNF-α |
| Mast cells | TNF, IL-1, IL-4, IL-6, IL-8, IL-10, IL-13, IFN-γ |
| Dendritic cells | IL-2, IL-4, IL-5, IL-12, INF-γ |
| Keratinocytes | IL-18, TNF, IL-1, GM-CSF, INF-γ, IL-33 |
| Melanocytes | INF-β, IL-1, IL-8, IL-10, TNF-α |
| Fibroblasts | IL-33, TNF, IL-6, IL-8 |

Th1, T helper 1; IFN-γ, interferon-γ; TNF, tumor necrosis factor; IL, interleukin; GM-CSF, granulocyte-macrophage colony stimulating factor.

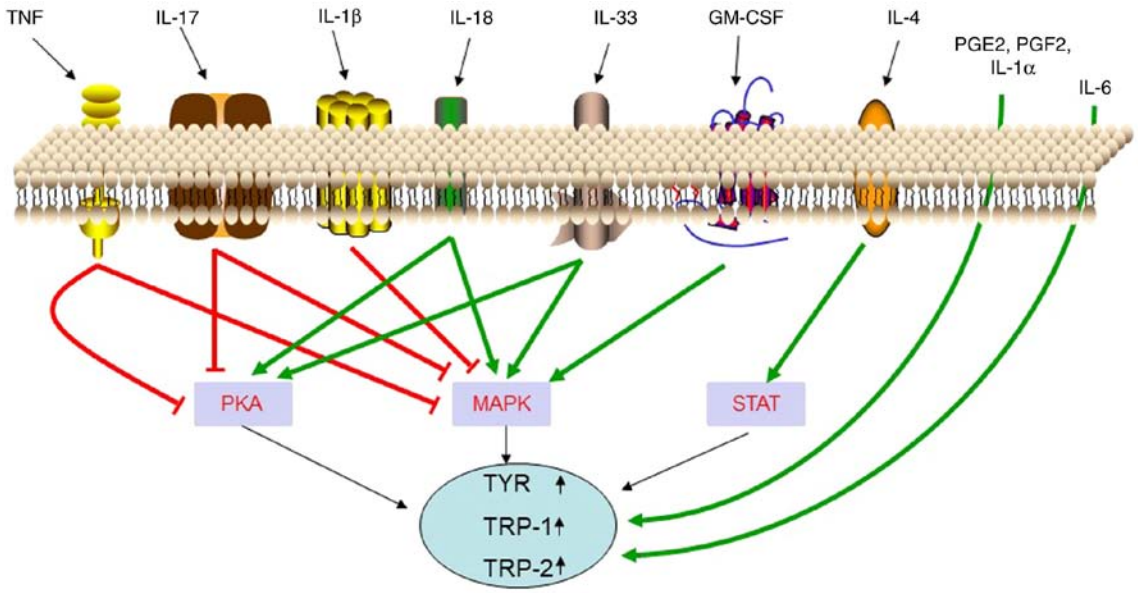


Figure 3. Cytokines that inhibit or stimulate melanogenesis. Cytokines such as TNF, IL-17 and IL-1β inhibit melanogenesis by suppressing the PKA or MAPK pathway. While cytokines such as IL-18, IL-33 and GM-CSF stimulate melanogenesis by stimulating the PKA or MAPK pathway. IL-4 stimulates melanogenesis by stimulating the STAT pathway. PGE2, PGF2, IL-1α and IL-6 stimulate melanogenesis through unidentified signaling pathways. TNF, tumor necrosis factor; IL-17, interleukin-17; IL-1β, interleukin-1β; IL-18, interleukin-18; IL-33, interleukin-33; GM-CSF, granulocyte-macrophage colony stimulating factor; IL-4, interleukin-4; PGE2, prostaglandin E2; PGF2, prostaglandin F2; IL-1α, interleukin-1α; IL-6, interleukin-6; PKA, protein kinase A; MAPK, mitogen activated protein kinase; STAT, signal transducer and activator of transcription; TYR, tyrosinase; TRP-1, tyrosinase-related protein-1; TRP-2, tyrosinase-related protein-2.

development is directly affected by the imbalance of the Th1/Th2 response (85). Nouri-Koupaee *et al* revealed the Th1 and Th2 response profiles in vitiligo by assessing IFN-γ and IL-4. This study revealed significant increases in IFN-γ and marked decreases of IL-4 in patients when compared to controls (86). It has also been revealed that IL-4 downregulates the expression of MITF, TYRP-1, and TYRP-2 through the JAK2/STAT6 signaling pathway and thus inhibits melanogenesis (13).

IL-6 is secreted by keratinocytes, epidermal cells, fibroblasts and dermal endothelial cells and is involved in the regulation of various biological responses including immune response, inflammation, hematopoiesis, and tumorigenesis by regulating cell growth, survival, and differentiation (87). Research has revealed that IL-6 decreases tyrosinase activity and melanogenesis (12).

IL-17 is a pro-inflammatory cytokine produced mainly by Th17 cells, and also by other immune cells, including neutrophils, natural killer cells, mast cells, αβ and γδT cells (88). The most well-known function of IL-17 is to prevent bacterial and fungal infections (88). IL-17 has a variety of inflammatory effects, resulting in the release of large amounts of cytokines from a variety of cells, such as epithelial cells, endothelial cells, and fibroblasts (89). Studies have revealed that IL-17 can bind to TNF to inhibit the signaling pathway for melanogenesis, thereby inhibiting melanogenesis (10). The function

Table II. Function and mechanisms of inflammatory factors in the regulation of melanogenesis.

| Factor | Experimental cells | Effect on melanogenesis | Mechanisms | (Refs.) |
|---|---|---|---|---|
| IL-18 | Keratinocyte | Promotion | Increasing tyrosinase activity and upregulating TYRP-1 and TYRP-2 expression | (43) |
| IL-33 | Melanocytes | Promotion | Promoting MITF, TYR, TYRP-1, TYRP-2 expression by activating the p38/MAPK and PKA pathways | (14) |
| GM-CSF | Melanocytes | Promotion | Promoting melanocyte proliferation and melanin synthesis | (17) |
| PGE2 and PGF2α | Keratinocytes | Promotion | Stimulating melanocyte dendrite formation through a cAMP-dependent pathway | (62) |
| IFN-γ | B16F10 | Inhibition | Blocking maturation of melanosome and upregulating STAT1 phosphorylation | (46,72) |
| TNF | Melanocytes, primary pooled human keratinocytes | Inhibition | Inhibiting melanin formation through PKA and MAPK signaling pathways in combination with IL-17 | (10) |
| IL-1α | Primary melanocytes, swine skin | Promotion | Combination of KGF increases melanin deposition | (79) |
| IL-1β | Melanoma cell lines (LB2259-MEL and CP50-MEL) | Inhibition | Downregulating MITF-M expression through NF-κB and JNK pathways | (74) |
| IL-4 | Melanocytes | Inhibition | Downregulating the expression of MITF, TYRP-1, TYRP-2 through the JAK2-STAT6 signaling pathway | (13) |
| IL-6 | Melanocytes | Inhibition | Decreasing tyrosinase activity | (12) |
| IL-17 | Melanocytes, primary pooled human keratinocytes | Inhibition | Inhibiting melanin formation through PKA and MAPK signaling pathways in combination with TNF | (10) |

TYRP-1, tyrosinase-related protein-1; TYRP-2, tyrosinase-related protein-2; MITF, microphthalmia-associated transcription factor; TYR, tyrosinase; PKA, protein kinase A; MAPK, mitogen activated protein kinase; JNK, c-Jun N-terminal kinase; JAK-STAT, Janus kinase-signal transducer and activator of transcription.

and mechanisms of these inflammatory factors in regulating melanogenesis are presented in Table II.

It should be noted that the IFN-γ-related data were acquired from a murine melanoma model (B16F10) and IL-1α-related data were based on observations from porcine skin. Therefore, whether their effects on melanogenesis in human melanocytes are the same still requires confirmation by subsequent experiments.

## 5. Post-inflammatory hyperpigmentations and hypopigmentations can be treated by regulating local inflammatory factors

In clinical practice, various treatments can be effective for post-inflammatory hyperpigmentations and hypopigmentations by influencing inflammatory factors. For example, chloasma is a postinflammatory hyperpigmented disease caused by many factors such as heredity, ultraviolet radiation, pregnancy, hormone therapy, cosmetics, and phototoxic drugs (90). Kojic acid, hydroquinone, and tranexamic acid are commonly used to treat melasma (91). It is well-known that their inhibitory effect on tyrosine activity or melanocyte-specific cytotoxicity is the decolorization mechanism (92,93). In recent years, it has been revealed that kojic acid also inhibits the melanogenesis of melanocytes by promoting the expression of IL-6 in keratinocytes. Resveratrol was revealed to play an important role in ameliorating inflammation, including skin inflammation and reducing inflammatory injury in HaCaT cells (94). Studies have also reported that resveratrol inhibits melanin synthesis to treat hyperpigmented diseases (95). Therefore, resveratrol may also affect melanogenesis by regulating inflammatory factors.

Although the causes of vitiligo are not completely clear, inflammation has been revealed to play a role in its pathogenesis (96). Certain studies revealed that higher expression of pro-inflammatory cytokines had an inhibitory effect on pigmentation in vitiligo lesions (97,98). For example, Kim *et al* (99) revealed that increased expression of TNF-α in keratinocytes of the lesion area in vitiligo patients inhibited the secretion of melanocyte growth factor from KCs. Barygina *et al* suggested that low-dose IL-4, β-endorphin, bFGF and IL-10 may be considered as new therapeutic tools for vitiligo treatment (100).

Studies have revealed that 308 nm excimer laser can significantly reduce the level of TNF-α in lesions (101), thereby promoting MC function. Various studies reported that the expression of IL-4, TNF-α and other inflammatory cytokines was down-regulated after topical application of tacrolimus in lesions of vitiligo (102,103). Methotrexate (MTX) is used in the treatment of autoimmune diseases to decrease T cells that produce TNF-α, which is a key step in the development of vitiligo (104). A study by Alghamdi and Khurrum revealed that oral MTX was a safe and effective therapeutic approach for vitiligo, however, due to the fact that this was a small uncontrolled pilot study, further research needs to be carried out (105). Afamelanotide is a potent and longer-lasting synthetic analogue of naturally occurring α-MSH, which is decreased in vitiligo. Grimes *et al* (106) found that NB-UVB combined with afamelanotide is safe and effective and that afamelanotide represents a potentially effective treatment for vitiligo, however this still requires further studies. The aforementioned findings indicated that the external use of medications, light therapy and other treatments may serve to treat inflammation related-hyperpigmentations or hypopigmentations by regulating the expression of inflammatory factors associated with melanin production.

## 6. Conclusion and outlook

Studies have revealed that a variety of inflammatory factors can promote or inhibit the melanogenesis of melanocytes through different mechanisms, suggesting that the development of medicine or therapies from the perspective of inflammation regulation can provide new ideas and new targets for the treatment of pigmented dermatosis. It is widely considered that the regulatory network of inflammation is very complex, since all types of inflammatory cells are involved in the activation and release of inflammatory mediators. The imbalance of inflammatory factors related to T-cell subsets plays an important role in the development of various skin diseases, however, the relationship between imbalance or changes of T-cell subsets and melanogenesis has yet to be confirmed by further experiments.

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## Availability of data and materials

The datasets used during the present study are available from the corresponding author upon reasonable request.

## Authors' contributions

CF and JC designed and wrote the paper. JH and QZ designed and supervised the study. JL, LY, XT, LK, SP, YO, LJ, YD, XZ, SL and YY analyzed and interpreted the data. All authors have read and approved the final manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no interests.

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