3-20-2022

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Received: 6 November 2021 | Revised: 22 February 2022 | Accepted: 16 March 2022

DOI: 10.1111/pcmr.13038

REVIEW

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A Focused review on the pathophysiology of post-inflammatory hyperpigmentation

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Abstract

Post-inflammatory hyperpigmentation (PIH) is one of the most common disorders of acquired hyperpigmentation. It often develops following cutaneous inflammation and is triggered by various stimuli, from inflammatory and autoimmune conditions to iatrogenic causes and mechanical injuries. While it is well established that an increase in melanin production and distribution within the epidermis and dermis is a hallmark feature of this condition, the exact mechanisms underlying PIH are not completely understood. This article aims to review the current evidence on the pathophysiology of PIH as the cellular and molecular mechanism of PIH represents a promising avenue for the development of novel, targeted therapies.

KEYWORDS
growth factors, mesenchymal-epithelial cross-talk, post-inflammatory hyperpigmentation, skin of color

1 | INTRODUCTION

Post-inflammatory hyperpigmentation (PIH) is an acquired hypermelanosis and a common sequela of various inflammatory disorders. (Taylor et al., 2009) While the exact incidence remains unclear, worldwide prevalence of PIH is estimated to range from 0.42% to 9.99% in African Americans. (Davis & Callender, 2010) Although all skin types can develop PIH, it primarily affects patients with darker skin types (Fitzpatrick type III-VI). (Taylor et al., 2009) Due to the increased frequency and severity in individuals with darker skin, PIH often leads to psychosocial distress and decreased quality of life. (Darji et al., 2017) In a study conducted by Darji et al., the psychosocial impact of PIH on patients with acne was explored. Compared to patients with acne alone, those with concomitant acne and PIH had a significant impairment of all aspects of Acne Quality of Life (AQOL) (e.g., having difficulties with friends and partners, feeling self-conscious and isolated, feeling embarrassed). (Darji et al., 2017) In addition to acne, other triggers for PIH include atopic dermatitis, and impetigo. (Lawrence et al., 2021) Iatrogenic causes of PIH are not uncommon and include chemical peels and laser procedures. (Lawrence et al., 2021) As such, individuals with darker skin tones cannot receive certain treatments safely, leading to disparities in care.

Despite the high disease burden, treatment options for PIH are limited and data regarding their efficacy are sparse. Given the therapeutic challenge of PIH and its significant impact on quality of life, understanding the evolution of disease pathogenesis is of clinical importance to develop novel therapies. This review aims to describe the current understanding of PIH pathogenesis, including current PIH models, epithelial-mesenchymal cross-talk, the role of growth factors, and how dysregulation of skin homeostasis contributes to the development of PIH.

2 | DISCUSSION

2.1 | Histologic findings of PIH

Recent studies have suggested different histologic patterns of PIH based on skin layer involvement. (Nordlund & Abdel-Malek, 1988; Park et al., 2017) For PIH involving the epidermis, it is thought that hyperpigmentation results from an increase in the

number (hyperplasia), size (hypertrophy), and activity of melanocytes. Histologically, these cellular changes are characterized by an increase in epidermal melanin and with minimal dermal changes. (Nordlund & Abdel-Malek, 1988; Park et al., 2017) In cutaneous pathologies where the basement membrane zone is the major target, such as systemic lupus erythematosus and lichen planus, PIH forms following disruption of basal keratinocytes and subsequent deposition of melanin granules within the dermis. (Park et al., 2017) Clinically, this presents as slate-gray and/or blue-black pigmentation. Two major theories have been proposed explaining the presence of melanin within the dermis. The first theory considers melanocytes as the donor of melanosomes, which are directly deposited into the dermis through gaps in the basal lamina. In addition, it has been proposed that free melanosomes may be taken up by macrophages, which migrate to the dermis. The second theory postulates that abnormal keratinocytes along with their melanosomes undergo phagocytosis and are subsequently transferred to the dermis. The mechanism by which dyskeratosis occurs has been studied in hyperpigmentation secondary to fixed drug reaction, where lymphocytic infiltration in the epidermis activates downstream immune signaling pathways. (Masu & Seiji, 1983) Dyskeratotic keratinocytes contain mainly condensed tonofilaments, nuclear chromatin, and melanosomes. Dyskeratotic cells and melanosomes become engulfed by macrophages. Melanosome-laden macrophages are known as melanophages. These melanophages migrate and deposit in the dermis, contributing to dermal pigmentation. (Masu & Seiji, 1983; Park et al., 2017).

In addition to the presence of melanophages in the dermis, dermal PIH may be accompanied by a perivascular lymphocytic infiltrate, intense pigmentation in the upper dermis, and a decrease in epidermal pigmentation. (Masu & Seiji, 1983; Park et al., 2017) Despite limited treatment options for PIH, distinguishing between epidermal and dermal PIH is of clinical importance as it can guide treatment selection. Usually, dermal PIH is more difficult to treat than epidermal PIH as topical treatments, such as hydroquinone, azelaic acid, and other botanicals, mainly target decreasing melanin production, which does not affect dermal pigment that has already been deposited. (Davis & Callender, 2010) Although laser therapy (e.g., Picosecond and Q-switched lasers) is increasingly being utilized to treat dermal PIH, the reported success rates have varied significantly between published studies. (Kohli et al., 2020; Kovacs et al., 2010) Targeted treatments such as those that can facilitate the clearance of dermal melanophages and melanosomes are needed to address the dermal component of PIH.

It is important to note that recent studies have highlighted the limitations of using histology as an outcome measure for the evaluation of pigmentary changes. In a study conducted by Kohli et al., (Byun et al., 2016) in which pigmentation was induced by UVA (with or without visible light) on dark skin individuals (Fitzpatrick: III-VI) and was confirmed with objective measurement such as spectroscopy, histologic markers of pigmentation (e.g., Melanoma-Associated Antigen recognized by T cells) were unable to detect significant changes between irradiated sites and control skin. (Byun et al., 2016) It is plausible that factors such as skin phototype, variation in spectrums of radiation, and radiation dose play a role in these conflicting results. As such, use of these specific histologic markers could preclude a comprehensive and an accurate histologic examination of skin pigmentation and highlights the need to examine the utility of other histologic markers in the evaluation and diagnosis of PIH.

2.2 | Current In vivo models of PIH

2.2.1 | In Vivo models

In vivo models are central for evaluating disease pathogenesis, testing novel therapies, and determining treatment efficacy. Exploring the pathophysiology of PIH is a challenge owing to limited in vivo-specific PIH models, but a few human and animal models have been developed and validated.(Isedeh et al., 2016; Nakano et al., 2021; Passeron et al., 2018; Vellaichamy et al., 2022) These studies are discussed below and are summarized in Table 1.

2.2.2 | Trichloroacetic acid induced PIH in vivo model

Isedeh and colleagues (Isedeh et al., 2016) were the first group to validate an in vivo human model for acne-induced PIH through application of 35% trichloroacetic acid. While the use of 35% TCA resulted in PIH comparable to acne-induced PIH, this concentration of TCA resulted in epidermal necrosis. (Isedeh et al., 2016) To refine this model and determine the optimal concentration of TCA needed to induce PIH comparable to acne-induced PIH as well as minimize epidermal necrosis, multiple TCA concentrations (20%,25%, 30%, and 35%) were tested.(Vellaichamy et al., 2022) The study found that a concentration of 30% TCA was ideal for developing PIH similar to acne-induced PIH while minimizing epidermal necrosis. The second aim of this study was to explore the role of microRNAs (miRNA) in PIH development, given that they modulate melanogenesis. (Passeron et al., 2018) A comparative analysis of miRNA expression patterns revealed 21 miRNA exhibiting significant differences in expression levels between normal skin and TCA-induced PIH.

Authors from this study identified higher expression of miR-31-5p and miR-31-3p in TCA-induced PIH lesions. It has been shown that miR 31 promotes activation of nuclear factor kappa-light-chain enhancer of activated B cells (NF-KB) pathway. NF-KB signaling is involved in the eicosanoids pathway. The latter participates in an inflammatory cascade that has been shown to contribute to PIH pathogenesis. (Passeron et al., 2018) As such, findings from this study are promising and highlight the diagnostic and therapeutic potential of miRNA in PIH.

TABLE 1 Summary of published in vivo and in vitro studies examining the mechanism of post-inflammatory hyperpigmentation

Author, year	Experiment Design	Subjects	Treatment methodology	Major Findings
Isedeh et al., 2016	Human In vivo PIH model	30 healthy adult subjects (SPT II-VI) with truncal acne were recruited.	35% TCA applied to buttock skin for 30 seconds or until the skin showed signs of frosting. Lesions were monitored on Days 0, 1, 7, 14, 28, 42, and 56.	On Day 28: TCA-induced PIH showed histologic similarities with acne-induced PIH: -Perivascular lymphocytic infiltrate. -Dermal fibrosis. No significant difference in the number of melanocytes and dermal melanophages between acne-induced PIH and TCA-induced PIH samples ($p > 0.05$)
Vellaichamy et al., 2022	Human In vivo PIH model	29 healthy adult subjects (SPT II-VI) with truncal acne were recruited.	TCA at various concentrations (20%, 25%, 30%, and 35%) was applied to buttock skin and repeated applications were made until clinical frosting appeared (mean number of passes was five). Lesions were monitored on Days 0, 1, 7, 14, 28, and 35.	30% TCA application was shown to be the optimal concentration to induce PIH without inducing epidermal necrosis. - In TCA-induced PIH, miR−31-5p, miR−31-3p, and miR−23b−3p were expressed at significantly higher levels compared to normal skin (p value <0.001).
Passeron et al., 2018	Human In vivo PIH model	10 adults subjects (SPT IV-V) were recruited	Suction blisters applied to the inner part of forearm. From Day 0 to Day 5, treated area was covered with a total light block dressing blocking UVR and VL.	Histologic findings of PIH induced lesions: -Increase in tyrosinase staining – Increase in epidermal melanin. - Pigmentary incontinence, vascular proliferation, and neutrophilic infiltrate.
Nakano et al., 2021	Animal In vivo PIH model	5 Mice aged 16–20 weeks	DNFB used to induce ACD). 0.5% of DFNB was repeatedly applied to dorsal skin of each mouse for a total of nine times. Skin biopsies were then taken at Weeks 0, 1, 2, and 8.	At Week 2: DNFB skin demonstrated histologic findings similar to human PIH: -Increase in number of melanophages and epidermal melanin. - Redistribution of melanin-containing cells from the papillary dermis to reticular dermis. -Increase in dermal mast cells. -Within melanophages, DOPA staining was negative for tyrosinase, which suggests that melanin synthesis does not occur in phagocytosed melanosomes.
Tomita et al., 1992	In vitro	Subjects (SPT III-VI)	Using suction blister on normal skin, human melanocytes were extracted and cultured.	LTC4, LTD4 TXB2 increased TYR protein, cell perimeter, cell area, and number of dendrites.

Abbreviations: DNFB, 2,4, dinitrofluorobenzene; DOPA, dihydroxyphenylalanine; LTC4/D4, Leukotrienes C4/D4; miR, microRNAPIH; post-inflammatory hyperpigmentation; SPT, Fitzpatrick; TCA, trichloroacetic acid; TXB2, thromboxane B2; TYR, tyrosinase; UVR, ultraviolet radiation; VL, visible light.

2.2.3 | Suction blister induced PIH in vivo model

Passeron and colleagues (Passeron et al., 2018) also developed a human in vivo model using suction blisters, which yielded clinical and histologic findings consistent with PIH. Furthermore, in skin areas where suction blisters were induced, PIH was prevented when the treated area remained protected from all solar radiation, including visible light (VL), using an opaque dressing for 15 days. (Passeron et al., 2018) This finding highlights the role of UV and VL in triggering PIH. (Passeron et al., 2018).

2.2.4 | In Vivo animal model

Nakano and colleagues (Nakano et al., 2021) remain the only group that has developed an in vivo animal model that is clinically and histologically similar to PIH. The authors used a mouse model to induce PIH through the induction of chronic allergic contact dermatitis using 2,4 dinitrofluorobenzene. Histopathologic findings were notable for epidermal hyperplasia, inflammatory infiltrate in the dermis, and increased epidermal and dermal melanin. (Nakano et al., 2021) Melanin distribution varied based on location and time from PIH formation. (Nakano et al., 2021) In the epidermis, there was a significant reduction of melanin at Week 2 whereas the distribution of dermal melanin remained elevated throughout Week 4. (Passeron et al., 2018) This may be attributed to the fact that dermal melanin is largely located within macrophages, resulting in delayed turnover. (Nakano et al., 2021).

Although current in vivo PIH models are of clinical utility to enable more accurate testing and the development of new therapies, there continues to be a knowledge gap regarding the specific pathways involved in PIH. As such, it remains essential to develop in vitro PIH models that can be used to shed light on the molecular and cellular mechanism of the disease.

2.3 | Pathways contributing to PIH

2.3.1 | Inflammatory mediators

Early research has identified two distinct pathways by which PIH develops. Tomita and colleagues (Tomita et al., 1992) demonstrated that increased production of arachidonic acid metabolites, including leukotrienes (LTC4 and LTD4), prostaglandins (PG), and thromboxane (TX), promote melanogenesis through an increase in tyrosinase-related protein (Table 1). (Tomita et al., 1992) In the same study, human melanocytes (hMC) were treated with various arachidonic derivatives and it was shown that LTC4, LTD4, and TXB2 increased the activity of TYRP-1 protein as well as the cell perimeter (a measure of the degree of cell spreading), cell area, and number of dendrites. LTB4 and LTE4 also increased the amount of TYRP-1 protein and melanocyte perimeter, but with no change to the cell area and dendricity.

PGs represent a heterogeneous group of phospholipids involved in cellular growth, differentiation, and apoptosis. (Gledhill et al., 2010) Both inflammatory reactions and UV light exposure induce the production and upregulation of prostaglandins. (Gledhill et al., 2010; Kabashima et al., 2007) Several studies have reported the role of PGs as paracrine factors for melanocytes. Among the PGs, PGE-2 and PGF2α are the most abundant in the skin and their effects are mediated through G-protein coupled receptors, also known as EP receptors. PGs have a low affinity for EP1 and EP2 receptors and a strong affinity for EP3 and EP4 receptors. (Gledhill et al., 2010; Kabashima et al., 2007) In an in vitro study conducted by Scott et al., (Gledhill et al., 2010) it was demonstrated that hMC express both EP1 and EP3 receptors (receptors for PGE-2) and FP receptors (receptors for PGF2α). The activation of these receptors by their respective ligands can increase the dendricity of melanocytes. (Gledhill et al., 2010) The increase in melanocyte dendricity facilitates melanosome transfer from melanocytes to keratinocytes. (Gledhill et al., 2010) Nitric oxide (NO), which is generated in keratinocytes following UV light exposure, is a byproduct of oxygen metabolism and is implicated in melanin synthesis. (Starner et al., 2010) Through activation of intracellular guanylate cyclase, NO upregulates tyrosinase activity and tyrosinase-related protein-1, resulting in melanin synthesis that is regulated through a paracrine feedback loop. (Starner et al., 2010) Histamine is also considered a melanogenic factor, and its release from dermal mast cells appears to be mediated by UV irradiation. (Tse, 2010) A recent study conducted by Nakano et al. (Nakano et al., 2021) revealed the prominent distribution of dermal mast cells in PIH lesions, highlighting its potential role in disease pathogenesis. In addition, mast cells can directly induce melanogenesis by secreting IL-33. The latter promotes the expression of MITF and TYR proteins, which are involved in melanogenesis. (Chan et al., 2008) Thus, the role of both mast cells and histamine in PIH pathogenesis merits further investigation.

2.3.2 | Cross-talk communication signaling pathway

While no specific studies exploring the cellular and molecular mechanism of PIH exist, it is important to appreciate the pathways involved in cutaneous pigmentation.

Skin pigmentation relies on a complex interplay between keratinocytes and melanocytes. (Roméro-Graillet et al., 1996) The cross-talk signaling pathway is mediated via paracrine effects involving the secretion of keratinocyte-derived soluble factors including α-melanocyte-stimulating hormone (α- MSH), endothelin 1 (ET- 1), stem cell factor (SCF), hepatocyte growth factors (HGF), and prostaglandin E2 and F2 alpha (PGE2, PGF2α). (Gilchrest et al., 1981) These keratinocyte-derived factors bind to their specific receptors, located on the melanocyte cell membrane, and activate various signaling pathways, such as the cyclic AMP/protein kinase A pathway, which are involved in the proliferation and differentiation of melanoblasts into melanocytes. (Hossain et al., 2021) Keratinocytes also modulate melanogenesis following ultraviolet (UV) irradiation.

(Cichorek et al., 2013) It has been shown that keratinocytes release various inflammatory cytokines including interleukins (IL)-18, IL-33, and granulocyte-monocyte colony stimulating factor (GM-CSF). (Gilchrest et al., 1981) IL-18, IL-33, and GM-CSF are responsible for the upregulation of tyrosinase-related protein 1 and 2 (TYRP 1 and 2), which promote melanogenesis. In addition, IL-18 can directly upregulate the activity of tyrosinase, a key enzyme in melanin production. (Gilchrest et al., 1981) Through a paracrine feedback loop, keratinocytes can indirectly stimulate the production of melanin via the release of tumor necrosis factor alpha (TNF-α),, IL-1β, and IL-6. These cytokines stimulate dermal fibroblasts, which in turn release melanocyte-stimulating factors including HGF, SCF, and keratinocyte growth factor (KGF) (Figure 1). (Cichorek et al., 2013) To prevent excess production of melanin, these same cytokines, via a negative feedback loop, regulate UV induced melanogenesis and inhibit melanogenesis by downregulating tyrosinase gene expression via activation of NF-KB. (Hossain et al., 2021)

In addition to UV light-induced melanogenesis, Randhawa et al. (Haass & Herlyn, 2005) used an ex vivo model to elucidate the pigmentation mechanism of VL. It was shown that repeat exposure to VL resulted in de-novo formation of melanin, which appeared to be mediated through an increase in tyrosinase activity.

2.3.3 | Role of growth factors in pigmentation

Although the role of the dermal compartment in pigmentation has been less extensively studied, there is increasing evidence supporting the role of mesenchymal cells (e.g., fibroblasts) in melanin production. (Hossain et al., 2021; Kapoor et al., 2020) Fibroblasts represent a heterogeneous group of mesenchymal cells that have been shown to influence skin pigmentation by secreting various growth factors including KGF, SCF, and basic fibroblast growth factor. (Hossain et al., 2021) Recent studies have demonstrated the role of growth factors in the pathogenesis of melasma and solar lentigines (SL). (Duval et al., 2012; Randhawa et al., 2015) While there is paucity of data regarding the role of growth factors in PIH pathogenesis, PIH shares some clinical and histologic features with melasma and SL. As such, findings from SL and melasma experimental studies may be helpful in elucidating the cellular mechanism by which growth factors contribute to the development of PIH.

In a study conducted by Hasegawa et al., and compared to normal skin, biopsied SL and melasma lesions exhibited a marked increase in KGFexpression. (Ceccarelli et al.,2005) In addition, KGF was predominantly distributed in the epidermis. Comparable

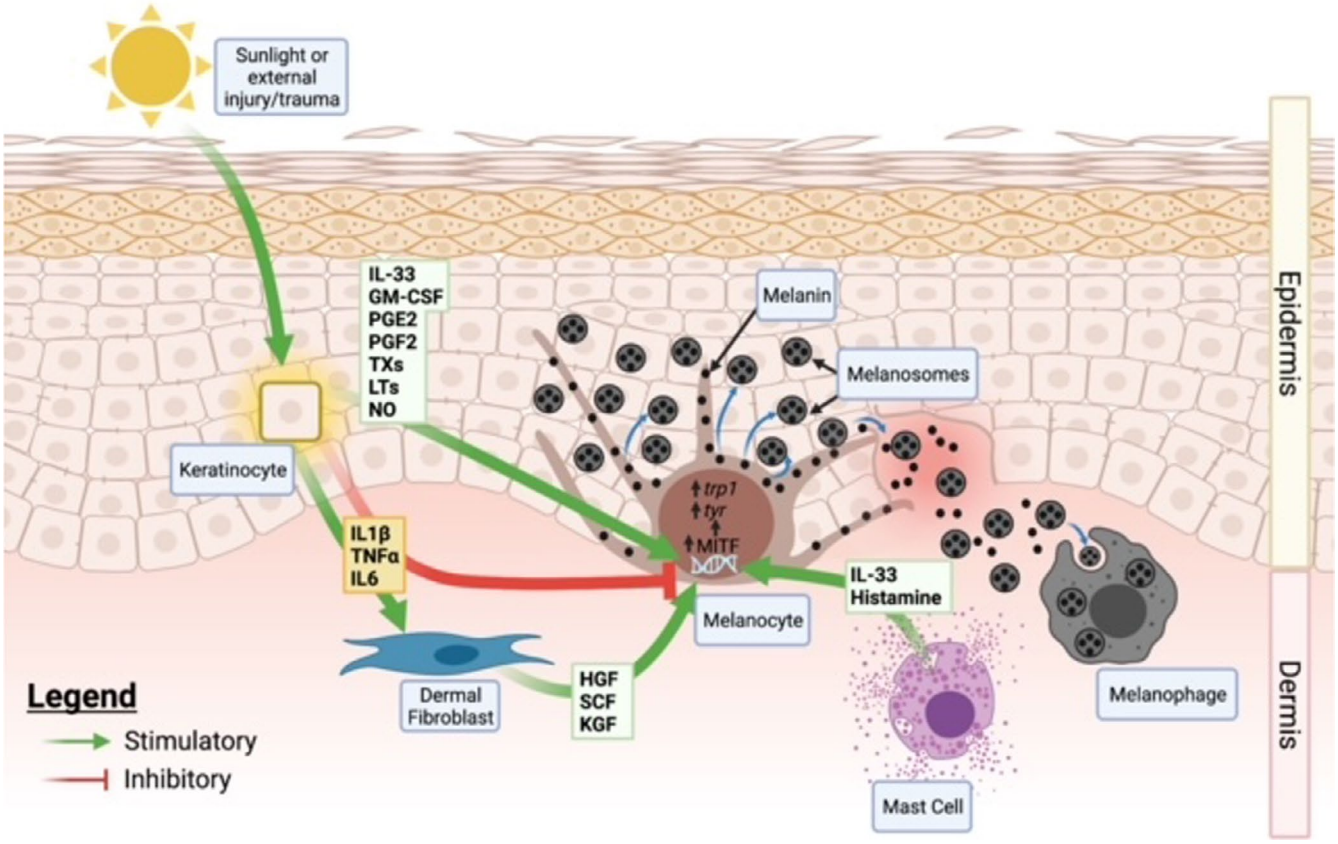

FIGURE 1 Diagram illustrating the proposed mechanism by which post-inflammatory hyperpigmentation (PIH) occurs. In this illustration, the major (proposed) pathways involved in PIH include the release of inflammatory cytokines from keratinocytes and growth factors from dermal fibroblasts. Following the production of melanin, its deposition in the dermis can occur in two ways, which are illustrated in this diagram: (1) Melanin can directly be deposited into the dermis through the gaps in basal lamina; (2) macrophages engulf melanin in the epidermis; these melanophages migrate from the epidermis to the dermis, which contribute to dermal pigmentation

results were shown by Lin and colleagues. (Hasegawa et al., 2015) In this study (Hasegawa et al., 2015), KGF expression was increased in facial SL lesions and was primarily distributed in both the epidermis and dermal fibroblasts. These findings highlight the role of the dermal compartment in the pathogenesis of hyperpigmentation. In addition, the level of expression of various growth factors (KGF, KGFR, SCF, and protease-activated receptor-2) appears to be influenced by the onset and progression of facial SL. (Hasegawa et al., 2015) Early lesions were characterized by melanin overload within keratinocytes due to high levels of KGF. The highest level of growth factor expression was seen in early to mid-stage lesions, and in late lesions, their expression was lower compared to normal skin.

In older lesions, the marked reduction in KGF levels affects both the proliferation and transfer of melanosomes to keratinocytes. It has been postulated that reduction of KGF reflects dormancy of keratinocytes; however, the higher expression of tyr protein, responsible for the production of tyrosinase, during late disease of SL suggests active melanocytes, which may explain the lifelong persistence of SL lesions. (Hasegawa et al., 2015) With regard to the physiologic functions of KGF, it has been proposed that KGF binds to KGF receptors located in phagosomes. (Kapoor et al., 2020) This interaction mediates the transfer of melanosomes from melanocytes to keratinocytes through phagocytosis. (Lin et al., 2010) As such, deregulation of KGF signaling appears to be primarily responsible for the clinical patterns seen in SL.

KGF has also been implicated in regulating plasminogen activator (PA). (Cardinali et al., 2005) PA is traditionally known for its role in hemostasis and thrombosis as it controls the formation and activity of plasmin, a key enzyme in fibrinolysis. (Tsuboi et al., 1993) The role of PA in melanogenesis is complex and involves multiple signaling pathways. (Castellino & Ploplis, 2005) Both tissue and urokinase-type PA are expressed in keratinocytes. (Chang et al., 1993) In an in vitro model, KGF was shown to have a stronger effect, relative to other growth factors, in stimulating the release of urokinase-type PA (uPA). (Rømer et al., 1991) The latter induces a dose-dependent increase in tyrosinase activity. (Lin et al., 2010) It has also been postulated that UV irradiation directly stimulates urokinase-type PA, which in turn activates plasmin activity in keratinocytes. (Zheng et al., 1996) The increase in plasmin levels results in upregulation of phospholipase A2 and subsequent activation of the arachidonic acid pathway, contributing to melanin synthesis. (Zheng et al., 1996) Tranexemic acid (TXA) is a fibrinolytic agent that specifically inhibits uPA activity and has shown promising results in the treatment of melasma. (Marschall et al., 1999) A recently published case report has documented the significant improvement in PIH lesions following the use of oral TXA acid. These findings demonstrate the therapeutic potential of TXA in the treatment of PIH and also highlight the role of plasminogen in PIH pathogenesis. (Bala et al., 2018).

Epidermal growth factor (EGF) is a ubiquitous protein involved in the growth, proliferation, and differentiation of keratinocytes and fibroblasts. (Lindgren et al., 2021) Recently, several studies have implicated EGF in melanin regulation. Although it was historically believed that melanocytes lacked EGF receptors (EGFR), an in vitro study (Bodnar, 2013) has demonstrated the wide expression of EGFR on melanocytes and suggested that EGF interferes with keratinocytes' ability to promote melanogenesis. In addition, EGF was shown to suppress tyrosinase activity. (Bodnar, 2013) These mechanisms have significant clinical implications as exemplified by a recently published study examining the incidence of PIH in patients who underwent QS 532 nm Nd:YAG laser treatment of SL. In this study, following Nd:YAG laser treatment, patients were randomly assigned to treatment with an EGF ointment or pertrolatum (control). (Yun et al., 2013) Compared to the control group, the use of topical EGF resulted in a significant reduction in the incidence of laser-induced PIH at Week 8 (37.5% vs 7.14% $p = 0.014$). (Yun et al., 2013) While rare, the use of EGFR inhibitors as a chemotherapeutic agent has been reported to induce hyperpigmentation, further supporting the possible role of EGF in the development of hyperpigmentation. (Chang et al., 2004; Kim et al., 2021)

3 | CONCLUSION

PIH remains one of the most common causes of hyperpigmentation and has a significant impact on patients' quality of life. In recent years, new PIH-specific in vivo models have emerged, representing a step forward in PIH research. The pathogenesis of pigmentation is complex, with contributions from multiple cell types, cytokines, growth factors, and cellular cross-talk. However, very few PIH-specific studies exist. These are necessary to further elucidate the pathogenesis of this condition and develop novel and targeted therapies for a dermatologic condition that continues to represent a therapeutic challenge.

CONFLICT OF INTEREST

Tasneem Mohammad is an investigator for Clinuvel, Incyte Corporation, Pfizer, Avita, Arcutis, Pierre Fabre, Estee Lauder, Unigen Inc., Ferndale Healthcare Inc., and Allergan. Iltefat Hamzavi is an investigator for PCORI, Incyte Corporation, AVITA medical, L'Oréal, Beiersdorf, Estee Lauder, Unigen Inc., Ferndale Healthcare Inc., Pfizer, Allergan, and Johnson & Johnson and has served as a consultant for Pfizer, Johnson and Johnson, and Beiersdorf. None of the remaining authors have any conflict of interest to disclose. Iltefat H. Hamzavi is an investigator for PCORI, Incyte Corporation, L'Oréal, Beiersdorf, Estee Lauder, Unigen Inc., Ferndale Healthcare Inc., Pfizer, Allergan, and Johnson & Johnson and has served as a consultant for Pfizer, Johnson and Johnson, and Beiersdorf.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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How to cite this article: Maghfour, J., Olayinka, J., Hamzavi, I. H., & Mohammad, T. F. (2022). A Focused review on the pathophysiology of post-inflammatory hyperpigmentation. *Pigment Cell & Melanoma Research*, *00*, 1–8. https://doi.org/10.1111/pcmr.13038