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Mechanisms underlying post-inflammatory hyperpigmentation: lessons from solar lentigo

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Summary
Hyperpigmentation of the skin is a common dermatologic condition in all skin types but most prominent in brown-skinned population. In skin of color any inflammation or injury can be accompanied by alterations in pigmentation (hyper/hypo-pigmentation). Post-inflammatory hyperpigmentation (PIH) can be observed in many skin conditions including acne, eczema, and contact dermatitis. In the control of skin pigmentation, parallel to the cross-talk between keratinocytes and melanocytes, increasing evidence has underlined the crucial role exerted by the interactions between mesenchymal and epithelial cells through the release of fibroblast-derived growth factors. Among these factors, the keratinocyte growth factor (KGF), alone or in combination with interleukin-1α, induces melanin deposition *in vitro* and hyperpigmented lesions *in vivo*. Furthermore, a moderate increase of KGF and a high induction of its receptor have been shown in solar lentigo lesions, suggesting the involvement of this growth factor in the onset of the hyperpigmented spots. Several studies highlight the possible contribution of the fibroblast-derived melanogenic growth factors to the hyperpigmentated lesions, in the context of the mesenchymal – epithelial interactions modulating melanocyte functions.

MOTS CLÉS
Hyperpigmentation post-inflammatoire ;
Mélanogenèse ;
Interaction derme épiderme et lentigo actinique

Résumé
Les hyperpigmentations cutanées sont une des dermatoses les plus fréquentes sur tout type de peau, mais ceci est particulièrement vrai dans les populations à peau foncée. Dans les phototypes foncés, toute inflammation ou traumatisme peut se traduire par des altérations de la pigmentation, qu'il s'agisse d'hyperpigmentations ou d'hypopigmentation. Les pigmentations post-inflammatoires peuvent être observées dans de nombreuses maladies cutanées, notamment l'acné, la dermatite atopique et l'eczéma de contact. On sait que le contrôle de la pigmentation résulte d'interactions entre les kératinocytes et les mélanocytes, mais il y a de plus en plus de données soulignant le rôle crucial des interactions entre les cellules mésenchymateuses et épithéliales, grâce à la production de

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facteurs de croissance par les fibroblastes. Parmi ces molécules, le facteur de croissance kératinocytaire (KGF), seul ou en association avec l'interleukine 1-α, peut provoquer des dépôts de mélanine *in vitro* et des lésions hyperpigmentées *in vivo*. De plus, on a montré que dans les lésions de lentigo actinique, il existe une augmentation modérée du facteur de croissance kératinocytaire et une importante induction de son récepteur ; ceci suggère un rôle de ce facteur de croissance dans l'apparition des taches hyperpigmentées. Plusieurs études ont souligné aussi l'importance des facteurs de croissance mélanocytaires produits par les fibroblastes dans la genèse des lésions hyperpigmentées, soulignant ainsi l'importance des interactions mésenchyme-épithélium dans le contrôle de la fonction mélanocytaire.

Introduction

Post-inflammatory hyperpigmentation (PIH) of the skin is a pigmentary disorder that is seen in all skin types, but remains a hallmark of skin of color [1]. In darker skinned individuals, any inflammation or injury to skin can be accompanied by alterations in pigmentation, either hyperpigmentation or hypopigmentation. PIH can be caused by endogenous inflammatory skin disorders or iatrogenic sources (lasers). It can be observed in many skin conditions including acne, eczema, and contact dermatitis and can be diffuse or localized, depending on the distribution of the preceding inflammation. PIH is characterized by increased melanocytic activities and dermal melanophages. This condition tends to be worse in patients whose preceding inflammatory disease, such as lichen planus and lupus erythematosus, has disrupted the basal layer of the epidermis [2]. A variety of topical agents are available to reduce the hyperpigmentation [3].

Cutaneous paracrine network in skin pigmentation

Human skin color is mainly due to melanin pigments produced by melanocytes and transferred to neighboring keratinocytes via their dendrites. Constitutive pigmentation depends on the quantity and the quality (pheo/eumelanin ratio) of the melanin produced, as well as the size, mode of transfer, distribution and degradation of the melanosomes inside the keratinocytes and not on the number of melanocytes which is relatively constant. Keratinocytes are also crucial in regulating the adhesion, proliferation, survival, and morphology of melanocytes. The cross-talk between melanocytes and keratinocytes is mediated by a paracrine effect through keratinocyte-derived soluble factors including α-melanocyte-stimulating hormone (α-MSH), endothelin 1 (ET-1), stem cell factor (SCF), basic fibroblast growth factor (bFGF), prostaglandin E2 and F2 alpha (PGE2, PGF2α), hepatocyte growth factor (HGF) [4,5]. Keratinocytes also modulate the transcription of melanogenic proteins and subsequently the quantity and quality of melanin [6]. Furthermore, keratinocytes, via the increase in numerous released cytokines, are strongly involved in the pro-pigmenting response of melanocyte after UV exposure [5,7-9]. Even though the role of the dermal compartment on pigmentation is far less documented, there is now evidence, that the mesenchymal compartment including fibroblasts and fibroblast-derived extracellular matrix (ECM) proteins, influences melanocyte proliferation, apoptosis resistance, morphology and melanogenic activity [10-15]. Dermal fibroblasts play a regulatory role in constitutive pigmentation through the secretion of soluble factors [14]. Some are specifically secreted by fibroblasts such as Dickkopf-1 (DKK1) which is responsible for the very light color of the palms and soles via a suppressive effect on melanocyte activity and melanin uptake by keratinocytes [13,15]. More recently, the pro-pigmenting effect of Neuregulin-1 secreted by fibroblasts derived from dark skin suggests its involvement in determining human skin color [11]. Furthermore, paracrine cytokines regulation loop also exist: keratinocyte-produced cytokines, such as interleukin-1 alpha (IL1-α) or TNF-α, stimulate fibroblasts which in turn release melanocyte stimulating factors such as SCF and HGF [16]. Deregulations of melanocyte homeostasis and/or melanogenesis are the cause of various hyper/hypopigmented lesions. For a better understanding of the pigmentation mechanisms and their deregulations, *in vitro* systems have been developed that reproduce the physiology of the pigmentary system. These models reproduce key structures of native skin especially a three-dimensional organization and a differentiated epidermis [17,18]. To overcome the absence of fibroblasts in these reconstructed epidermis, more complex organotypic pigmented skin models reconstructed on a dermal equivalent containing fibroblasts, have been designed [10,12,19-22]. In order to study human skin pigmentation in a highly physiological *in vitro* model, Duval et al. [23] have reconstructed a pigmented skin model, including human normal melanocytes, keratinocytes and fibroblasts able to develop a real constitutive pigmentation (melanin production and transfer) and able to respond to known stimulators. They demonstrated that the normalization of keratinocyte differentiation using KGF, a paracrine growth factor produced by mesenchymal cells allowed an active pigmentation, as shown by the expression of key melanogenic markers, the production and transfer of melanosomes into keratinocytes. Furthermore, induction of pigmentation was achieved by treatment with known pro-pigmenting molecules, α-MSH and forskolin, thus demonstrating the functionality of the pigmentary system. This pigmented skin model represents a useful tool to study the mesenchymal-epithelial interactions in the control of skin pigmentation.

Post-inflammatory hyperpigmentation

PIH represents the sequelae of inflammatory disease processes such as infections, allergic reactions, phototoxic eruptions and trauma [24]. PIH frequently appears after the regression of different inflammatory cutaneous disorders including lichen planus, lupus erythematosus, bullous pemphigoid, herpes zoster and more common skin diseases such as atopic dermatitis and acne vulgaris [2,25]. It is thought that PIH occurs through the oxidation of arachidonic acid by peroxidase, cyclooxygenase and 5-lipoxygenase to intermediates that form prostaglandins, leukotrienes and thromboxanes. These stimulate epidermal melanocytes to become hypertrophic, leading to increased synthesis of melanin and the transfer of pigment to surrounding keratinocytes and dermal macrophages. The result is the appearance of hyperpigmented lesions with indistinct, feathered borders that vary in size, shape and colour [26,27].

PIH is commonly induced by acne lesions, most prevalently in the darker Fitzpatrick skin types IV- VI [28-31]. Therefore, a major issue in treating acne in skin of colour is the need to treat and prevent PIH. Topical retinoids are considered a key component of the treatment regimen for acne vulgaris because they play a role in blocking the development of both acne and PIH [28,32-34].

Solar lentigo as a model of hyperpigmentary disorder

Melanocytes play an important role in the protection of skin from ultraviolet (UV)-induced damage by producing melanin whose synthesis is catalysed by melanogenic enzymes. Acute or persistent UV exposure evokes an inflammatory reaction including formation of topical oedema and erythema, which results in hyperpigmentation of skin as evidenced by formation of melasma, age spots, liver spots, freckles and lentigines. Therefore factors that mediate inflammation after UVB irradiation, such as bFGF, histamine, ET-1 and PGE2, are thought to be targets for developing skin-lightening agents after UV exposure. Solar lentigo (SL) is characterized by hyperpigmented lesions occurring in photodamaged skin areas which increase in number and size upon chronological ageing [35]. The histology of SL lesions reveals a hyperpigmented basal layer with an unchanged or slightly increased melanocyte number and an elongation of rete ridges above solar elastosis. Compared with perilesional skin, the basement membrane of SL lesions is disorganized, and their dermis contains more melanophages [36-39]. The molecular mechanisms involved in the initiation and formation of SL spots are not completely understood. Pigmentary proteins like tyrosinase (TYR), TYR-related protein-1, proopiomelanocortin, ET-1, endothelin receptor B and SCF and its receptor (c-KIT) are all increased in SL lesions [36,40-42]. Interestingly, two recent gene-profiling studies listed several inflammatory molecules that are up-regulated in SL [36,43]. The KGF binds to the KGF receptor (KGFR) which is expressed predominantly on epithelial cells, and mediates mesenchymal- epithelial interactions. It plays a role in wound healing [44] and in the regulation of hair follicle development. In addition, KGF acts on keratinocytes to induce melanosome phagocytosis [45]. This effect is more pronounced in light skin-derived keratinocytes, which express more KGFR than dark skin-derived keratinocytes [46]. Keratinocytes exposed to ultraviolet B (UVB) produce the inflammatory mediator IL-1α which in turn stimulates fibroblasts to produce KGF. Chen et al. [47] analysed the mechanisms involved in the initiation or in the maintenance of SL. They reported that KGF, alone or in combination with IL-1α, increases melanin deposition *in vitro* and induces hyperpigmentary lesions with elongated rete ridges *in vivo* with histological resemblance to human SL. Lin et al. [48] investigated the association of KGF/KGFR and pigmentary genes with the progression of SL development. An increase in TYR-positive cells and expression was found throughout SL progression, as compared to normal skin. The levels of KGF, KGFR, SCF, Ki67 (marker of proliferation) and protease-activated receptor-2 (PAR-2) varied during SL progression. Ki67, Keratin 15 (K15) and KGF/KGFR were significantly up-regulated at early-mid SL stages. The latest-stage SL expressed the lowest levels of KGF, KGFR, SCF, Ki67 and PAR-2. The increase in KGF levels might promote excessive melanosome transfer, resulting in melanin overloads within SL keratinocytes. The reduced KGF/KGFR levels in mature SL might affect both the proliferative and the phagocytic ability of the SL keratinocyte, further interfering with the melanosome transfer. The findings on the expression patterns of KGF/KGFR and other genes during SL macules development reflect on the molecular and cellular mechanisms involved in SL formation and maintenance. Intervention of these pathways, and in particular of the KGF pathway, might prevent the formation of new SL macules, slow SL progression and possible reverse the development of newly forming SL lesions. Studies focused on the alteration in the cytokine paracrine network known to regulate pigmentation, demonstrating the up-regulation of the ET-1 /ETB receptor cascade and of SCF in the SL lesional epidermis [41,42]. The tumour suppressor protein, p53, which promotes UV-induced pigmentation by transcriptional activation of proopiomelanocortin [49], has been shown to be involved in the formation of hyperpigmented spots through the regulation of melanogenic cytokine networks both in keratinocytes and in melanocytes [50]. Parallel to the cross-talk between keratinocytes and melanocytes, increasing evidence underlines the crucial role exerted by the interactions between mesenchymal and epithelial cells in the control of skin pigmentation through the release of fibroblast-derived growth factors. Cardinali et al. [45,46] have demonstrated that KGF stimulates melanosome transfer promoting the phagocytic process directly through KGFR activity and signalling on keratinocytes. Overexpression of SCF and HGF by fibroblasts has been demonstrated in hyperpigmentary disorders such as dermatofibroma and café-au-lait macules [51,52]. A positive staining for SCF, HGF and KGF has been demonstrated in fibroblasts of two cases of generalized, progressive dyschromatosis disorder [53]. Kovacs et al. [54] analysed the possible contribution of the fibroblast-derived melanogenic growth factors to the hyperpigmentation of SL, in the context of the mesenchymal- epithelial interactions modulating melanocyte functions. In particular they analysed the involvement of the HGF, KGF and SCF in SL hyperpigmentation evaluating whether the photoageing process occurring in fibroblasts could be responsible for the altered expression of these cytokines. Moreover they investigated a new possible role of KGF in regulating pigmentation through the specific induction of melanogenic cytokines by keratinocytes. Results

showed positive staining for HGF, KGF and SCF in the upper dermis of SL lesions and a significant induction of the three cytokines in photoaged fibroblasts. In addition KGF was able to specifically modulate the expression of SCF in keratinocytes. In conclusion, they suggest that fibroblasts may be persistently activated by UV exposure to release melanogenic growth factors and this inducible cytokine network acts both directly and indirectly through keratinocytes and may contribute to the hyperpigmentation of SL.

Conclusions

Several experimental and clinical data demonstrated that a considerable intercellular complexity exists between melanocytes and the other cell types proximal to them. Skin pigmentation is regulated by a complex melanogenic network in which both keratinocytes and fibroblasts synthesize growth factors and cytokines able to modulate melanocyte activities. Inflammatory conditions influence cutaneous pigmentation through the cytokine-induced activation of downstream signals able to stimulate melanogenic activity. Consequently this complex network has to be taken in consideration to develop new therapeutic strategies to treat hyperpigmentary disorders.

Conflicts of interest statement

G. Cardinali: none.
D. Kovacs: none.
M. Picardo: none.

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