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Review article

Precise role of dermal fibroblasts on melanocyte pigmentation

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ABSTRACT

Dermal fibroblasts are traditionally recognized as synthesizing, remodeling and depositing collagen and extracellular matrix, the structural framework for tissues, helping to bring thickness and firmness to the skin. However, the role of fibroblasts on skin pigmentation arouses concern recently. More is known about the interactions between epidermal melanocytes and keratinocytes.

This review highlights the importance of *fibroblast-derived* melanogenic paracrine *mediators in the regulation of melanocyte activities.* Fibroblasts act on melanocytes directly and indirectly through neighboring cells by secreting a large number of cytokines (SCF), proteins (DKK1, sFRP, Sema7a, CCN, FAP-α) and growth factors (KGF, HGF, bFGF, NT-3, NRG-1, TGF-β) which bind to receptors and modulate intracellular signaling cascades (MAPK/ERK, cAMP/PKA, Wnt/β-catenin, PI3K/Akt) related to melanocyte functions. These factors influence the growth, the pigmentation of melanocytes *via* the expression of melanin-producing enzymes and melanosome transfer, as well as their dendricity, mobility and adhesive properties. Thus, fibroblasts are implicated in both skin physiological and pathological pigmentation. In order to investigate their contribution, various *in vitro* models have been developed, based on cellular senescence. UV exposure, a major factor implicated in pigmentary disorders, may affect the secretory crosstalk between dermal and epithelial cells.

Therefore, identification of the interactions between fibroblasts and melanocytes could provide novel insights not only for the development of melanogenic agents in the clinical and cosmetic fields, but also for a better understanding of the melanocyte biology and melanogenesis regulation.

Contents

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1. Introduction

Dermal fibroblasts are traditionally recognized as synthesizing, remodeling and depositing collagen and non-collagen extracellular matrix (ECM), the structural framework for tissues, helping to bring thickness and firmness to the skin. They communicate with each other and neighboring cells by secreting a large number of cytokines and growth factors, playing a crucial role in skin physiology. In term of pigmentation, fibroblasts exhibit a great dynamic in the epidermal melanogenesis, and participate actively in the signal cross-talk between melanocytes and keratinocytes. Most of previous research studied the regulation of skin pigmentation by focusing on both melanocytes which synthesize melanin, and neighboring keratinocytes which receive and distribute the pigment in upper layers of the skin. Interest in fibroblasts has increased in recent years due to their ability to secrete melanogenic factors. This review outlines the role of dermal fibroblasts in constitutive pigmentation and in the development of pigmentary disorders.

2. Correlation between fibroblast and melanocyte pigmentation

Studies increasingly elucidated the significant role of fibroblast in pigmentation. Photoaged fibroblasts in reconstructed skin model stimulate pigmentation, including both melanin production and melanogenic gene expression, compared to unexposed fibroblasts [1]. In addition, Salducci et al. observed an increase of melanocytes number in reconstructed epidermis cultured with conditioned media of UVA-treated fibroblasts [2]. However, fibroblasts limit the spontaneous pigmentation of melanocytes in 3D-reconstructed with cells from patient of phototype I and II, suggesting a role of fibroblasts in the control of pigmentation [3]. Murine and human fibroblasts did not secrete the same melanogenic and mitogenic melanocyte factors, resulting in a different effect on pigmentation. It has been shown that fetal fibroblasts in reconstructed skin model induce dramatic increase of pigmentation compared to adult fibroblast, resulting in the elevation of melanogenic mediators from fetal fibroblasts. Tsuchiyama et al. found that multilineage-differentiating stress-enduring cells, distinct stem cells among human fibroblasts, could be reprogrammed into melanocytes. These Muse-derived melanocytes reside in the basal layer of epidermis in 3D-skin model, and acquire melanocytic functions. This technique should permit treatment of vitiligo by autologous transplantation [4]. Moreover, Yang et al. successfully converted mouse and human fibroblasts to functional melanocytes by combination of several transcriptional factors, Microphthalmia-associated transcription factor (MITF), paired domain and homeodomain-containing transcription factor 3 (PAX3) and SRY-related transcription factor 10 (SOX10) [5]. These induced-melanocytes produce melanosomes and melanin, deliver melanin to keratinocytes in 3D-skin model and, even generate pigmentation *in vivo*. They may provide a new efficient way to treat melanogenic dysfunctions. Therefore, all these findings confirm an important cross-talking between fibroblasts and melanocytes in pigmentation. Specifically, these are fibroblast-derived secreted factors which are involved in the fibroblast interactions with melanocytes.

3. Signaling pathways of fibroblast-derived factors in melanocytes

As known, the pigment melanin including different types, pheomelanin and eumelanin, is produced by melanocytes in a complex process called melanogenesis: melanin synthesis in melanocytes, melanin transport from melanocytes to keratinocytes by melanosome, and melanin distribution in epidermis. All factors related to this process can affect melanin synthesis, including structural proteins of melanosome (Pmel17, MART-1, GPNMB), enzymes required for melanin synthesis (tyrosinase (TYR), tyrosinase-related protein-1 (TYRP-1) and dopachrome tautomerase (DCT)), and proteins necessary for melanosome transport and distribution (Rab27A, myosin Va, Slac2-a/melanophilin). MITF plays a significant role in melanogenesis and melanocytes differentiation, dendricity, proliferation and apoptosis. Specifically, MITF regulates the expression of melanogenic enzymes (TYR, TYRP-1 and DCT), melanosomal matrix (Pmel17, Rab27) and anti-apoptotic proteins (bcl-2). Signaling pathways play a key role in relaying extracellular signals from factor binding to cell membrane receptor to cell nucleus *via* a cascade of phosphorylation events. Four crucial intracellular signaling pathways regulate melanocyte functions, and three of them are associated with the expression and function of MITF [6,7].

3.1. MAPK/ERK

MAPK/ERK (mitogen-activated protein kinases/extracellular signal-regulated kinases) signaling is essential to the proliferation

and differentiation of melanocytes. The kinases MEK and ERK in MAPK signal transduction pathway involve the activation of melanocyte receptors *via* ligand binding to their extracellular domain (eg, receptor tyrosine kinase c-Kit) [8]. With binding to their receptors, ligand activates complex mechanisms (Ras-Raf-MEK-ERK) that lead to up-regulate MITF [9,10]. A mutation in the gene that encodes the RAF kinase BRAF leads to constitutive activation of downstream signaling in the MAP kinase pathway [11,12].

3.2. Wnt/β-catenin

Wnt/β-catenin signaling is another important pathway in pigmentation process and melanocytes differentiation, also for melanocyte stem cell [13–15]. Activation of Wnt/β-catenin signaling occurs upon binding of Wnt to frizzled receptors and lipoprotein receptor-related protein 5 and 6 (LRP5/6). Signals are transduced through the inhibition of glycogen synthase kinase-3β (GSK-3β) activity, leading to stabilization and transport of β-catenin into the nucleus, where it regulates transcription of MITF through interactions with lymphoid enhancer-binding factor (LEF). Wnt signaling is modulated by secreted and transmembrane Wnt inhibitors and activators [16].

3.3. cAMP/PKA

cAMP/PKA (cyclic adenosine monophosphate/protein kinase A) signaling can also contribute to MITF expression. Activation of some melanocyte receptors with their ligands (eg, melanocortin receptor MCR-1) results in increased levels of intracellular cAMP and activation of PKA [17]. PKA phosphorylates cAMP responsive element binding protein (CREB) which acts as a transcription factor of MITF. It has also been reported that activation of PKC can be associated with cAMP-dependent pathway [18]. Various intrinsic and extrinsic factors affect melanogenesis through this signal transduction pathway. They exert their actions directly on melanocytes or indirectly via mediators produced by surrounding skin cells [18,19].

3.4. PI3K/Akt

PI3K/Akt (phosphatidylinositol 3′-kinase/Akt) signaling pathway plays a critical role in melanocyte proliferation and apoptosis through the cell cycle regulation with GSK-3 and protein cyclin D1 [20,21], and the control of the proapoptotic protein BAD [22,23]. It could also cooperate with Ras-Raf-MEK-ERK signaling cascade on regulating melanocyte activity.

4. Fibroblast-derived factors involved in melanocyte activity

Fibroblasts release melanogenic factors which act both directly and indirectly on melanocytes. Numerous mediators secreted from fibroblasts play significant roles in the process of skin pigmentation through different signaling pathways. Some are involved in down-regulation (DKK1), modulation (sFRP) and induction (KGF, NRG-1) of pigmentation, some are involved in induction of proliferation and survival (SCF, bFGF, NT-3, Sema7a, TGF-β, CNN, FAP-α), and some are universal contributor (HGF) (Table. 1).

4.1. Inhibiting factor

4.1.1. DKK1

Dickkopf (DKK) family comprises 4 members (DKK1-4), and encodes secreted proteins that antagonize Wnt signaling by inhibiting Wnt coreceptors Lrp5 and 6. It takes part in numerous processes as bone formation, Alzheimer's disease, eye development and also skin pigmentation. DKK1 is produced by fibroblasts in skin and its regulatory role in melanogenesis was firstly described in 2004. Yamaguchi et al. reported that melanocyte density in palmoplantar human skin was five times lower than that in nonpalmoplantar part. Fibroblasts express highly levels of DKK1 mRNA on the palms and soles, and highly levels mRNA of DKK-3 in nonpalmoplantar area [24]. In further study, Yamaguchi et al. proved that DKK1 has an inhibitory effect on MITF expression which results mainly from the decreased activity of GSK-3β and β-catenin [25]. In addition, DKK1 up-regulates the expression of myoactive tetradeca peptide (MATP) which reduce TYR activity [26]. Therefore, DKK1 acts on melanocytes by suppressing proliferation and melanin production. These combined effects explain the lower pigmentation observed on the palms and soles.

4.2. Modulating factor

4.2.1. sFRP

Secreted frizzle-related protein (sFRP) family consists of 5 secreted proteins in humans (sFRP1-5) that modulate Wnt signaling by binding Wnt proteins and Frizzled receptors. Early studies found that sFRP binding to Wnt prevented the activation of Wnt receptors, leading to the initial classification of sFRPs as Wnt signaling inhibitors [27,28]. However, subsequent finding has suggested that sFRP2 functions as a melanogenic stimulator through Wnt/β-catenin signaling, but the precise mechanism needs to be clarified [29]. Kim et al. highlighted a certain paracrine role of fibroblast-derived sFRP2 in pigmentation. A co-culture experiment with sFRP2 over/downexpressed fibroblasts

Table 1
Effects of fibroblast-derived factors on melanocyte functions.

Fibroblast-derived factors	Melanocyte Receptors	Signaling Pathways	Targets	Effects on melanocyte functions
Dkk1	Frizzle	Wnt/β catenin	LEF-1	Down-regulation of pigmentation
sFRP	Frizzle	Wnt/β-catenin	LEF-1	Modulation of pigmentation
KGF	FGFR	MAPK	CREB	Induction of pigmentation
NRG-1	ErbB	MAPK, PI3K-Akt	CREB	Induction of pigmentation
SCF	C-kit	MAPK	CREB	Induction of proliferation, survival
bFGF	FGFR2	MAPK	CREB	Induction of proliferation, survival
NT-3	TrkC	MAPK, PI3K-Akt	CREB	Induction of proliferation, survival
Sema7a	PlexinC1	LIMKII	–	Induction of proliferation, survival
	β-integrin	MAPK,FAK	CREB	
TGF-β	TGFR	PKA	PAX3	Induction of proliferation, survival
		Smad	CREB	
CCN	CCNR	–	–	Induction of proliferation, survival
FAP-α	FAPR	FAK	–	Induction of proliferation, survival
HGF	C-met	MAPK	CREB	Universal contributor

demonstrated that fibroblast-derived sFRP2 increased pigmentation in normal human melanocytes. Thereby, the term of Wnt-signaling modulator is preferentially attributed to sFRP. Wnt inhibitory factor-1 (WIF-1) belonging to sFRP family is also an agonist of Wnt signaling pathway. It was shown that WIF-1 increases pigmentation in melanocytes co-cultured with WIF-1 overexpressed fibroblasts [30].

4.3. Activating factors

4.3.1. KGF

The keratinocyte growth factor (KGF) derived from fibroblasts participates in melanogenesis process by inducing melanosome transfer. Interleukin-1 α (IL-1α), an inflammatory mediator produced by keratinocytes after UVB exposure, stimulates fibroblasts to generate KGF. In synergy with cAMP, transferrin, ET-1 and bFGF, KGF increases differentiation, cell body expansion, dendrites extension and melanosome transfer [31]. In addition, KGF alone or in synergy with IL-1α and bFGF, induces melanin deposition and elongated rete ridges [32].

4.3.2. NGR-1

Neuregulin-1 (NRG-1), a nerve growth factor related to the differentiation and migration of neurons, is expressed differently among skin phototypes, and visibly increases skin pigmentation [33]. A higher level of NRG-1 is expressed in 3D-skin equivalents included fibroblasts from type VI (dark skin). In addition, the amount and size of melanocytes, as well as thickness of dendrites are increased [34]. NRG-1 binds specifically to ERBB3 and ERBB4 receptors and activates PI3 K and MAPK signaling pathways in melanocytes [35].

4.3.3. SCF

The cytokine stem cell factor (SCF) is secreted constitutively by fibroblasts. The soluble form secreted from fibroblasts binds to the c-kit receptor of melanocytes and activates the MAPK/ERK signaling pathway. SCF increases proliferation and differentiation of melanocytes with or without factors produced by keratinocytes, as cAMP, ET-1 and bFGF [36]. However the absence of SCF is correlated to a dysfunction of melanocyte proliferation. The signaling SCF/c-kit is necessary to the viability of melanocytes. The use of an antibody neutralizing c-kit (ACK2) induces apoptosis of murine melanocytes [37].

4.3.4. bFGF

The basic fibroblast growth factor (bFGF, FGF2), a member of the fibroblast growth factor family, is synthesized by fibroblasts and acts in a paracrine manner on melanocytes via its transmembrane receptor FGFR2 and the intracellular signaling MAPK pathway. bFGF is mitogenic and melanogenic for melanocytes [38].

4.3.5. NT-3

Neurotrophin-3 (NT-3) belongs to a family of nerve growth factors, synthesized by fibroblasts. These factors have been extensively studied for their role in the development of neurons and neural crest-derived cells such as melanocytes. NT-3 can link each Trk receptor including Trk-A, Trk-B and Trk-C, but mainly plays a biological function by binding to Trk-C. It modulates intracellular signal transduction through MAPK and PI3K-Akt pathways, regulating melanocyte differentiation and survival respectively [39].

4.3.6. Sema7a

Semaphorin 7a (Sema7a) from semaphorin family, a large class of secreted and membrane anchored proteins that is involved in numerous biological processes, stimulates dendrite outgrowth from melanocytes. Sema7a is a paracrine and UV irradiation-inducible ligand expressed by fibroblasts [40]. Plexin C1 and β1-integrins receptors are ligands for Sema7a, and signaling by these receptors has opposing effects on Sema7a-induced dendrite formation. Sema7a induces focal FAK and MAPK activation via β1-integrin, and stimulates melanocyte spreading and dendricity in human melanocytes. It regulates negatively melanocyte dendricity via the receptor Plexin C1.

4.3.7. TGF-β

The Transforming growth factor-β (TGFβ) family regulates a multitude of cellular processes, including cell survival, proliferation and apoptosis [41]. It is secreted from various cells including fibroblasts. After binding to its type I and II cell surface receptors, TGF-β activates smads signaling cascades. TGFβ signaling has been shown to exhibit a repressive effect on both melanocyte differentiation and melanogenesis *via* downregulation of MITF and PAX3, and to influence quiescence of melanocyte stem cells [42–44]. It is interesting that both TGFβ1 and TGFβ2 are upregulated by PAX3, and PAX3 itself is repressed by TGFβ1, suggesting a negative feedback mechanism. On the other hand, TGFβ reduces CREB-dependent transcription of MITF by repression of PKA [45]. In terms of paracrine action, TGF-β is a potent inhibitor of HGF secretion from fibroblasts.

4.3.8. CCN

The CCN family is a group of multifunctional secreted proteins designated CCN1 to CCN6. CCN proteins regulate crucial biological processes by connecting cell surface and ECM. Although they appear not to have specific high-affinity receptors, they signal through integrins and proteoglycans. CCN2 and CCN5 are mostly expressed in the dermis [46,47]. CCN1 is increasingly associated with age growth [48]. A role in skin pigmentation has been recently discovered. UV radiation upregulates CCN1-2 whereas CCN3-6 are downregulated [49].

4.3.9. FAP-α

Fibroblast activation protein-α (FAP-α), a member of serine protease family, is selectively expressed in fibroblasts. It plays an important role on tumor spreading and is highly expressed after UVR treatment [50]. This process could be upregulated by platelet derived growth factor-BB (PDGF-BB), TGF-β1, signaling protein Wnt5a released from melanocytes and plasminogen activator from melanoma cells [51,52].

4.3.10. HGF

The hepatocyte growth factor (HGF, also known as scatter factor), highly expressed by fibroblasts, binds to melanocyte receptor c-MET and triggers the MAPK and the PI3K-Akt signaling pathways, modulating melanocyte proliferation, migration, and melanogenesis [53,54]. The MAPK activates the ribosomal S6 kinase (RSK) family and improves the phosphorylation of CREB protein. The secretion of HGF is stimulated by keratinocyte cytokines, IL-1α and tumor necrosis factor-α (TNF-α) [55].

5. Fibroblasts in the development of pigmentary disorders

Alteration in melanin production is the fundamental change in pigmentary disorders of the skin, which can be caused by defects of melanocytes, keratinocytes and fibroblasts. Pigmentary anomalies can be classified according whether the pigment melanin is increased (lentigo, melasma, café-au-lait macules) or decreased (vitiligo), with localized or generalized distribution (Table2).

The earlier scientists thought that keratinocytes play the leading roles in pigmentation, and fibroblasts have quite few influence on pigmentation. For example, membrane-bound SCF

Table 2
Some common pigmentation disorders involving fibroblast-derived factors.

Skin pigmentary lesions	Clinical characteristics	Melanocyte features	Fibroblast-derived factors
Melasma	Hyperpigmentation Grey-brown patches	↗ Melanin synthesis ↗ Melanin transfer Apoptosis	SCF, CNN, NGF-β
Solar lentigo	Hyperpigmentation Brown spots and freckles	↗ Melanin synthesis ↗ Melanin transfer ↗ Dendricity ↗ Proliferation	SCF, HGF, KGF
Melanoma	Hyperpigmentation Tan, brown, black asymmetrical shape moles	↗ Melanin synthesis ↗ Proliferation ↗ Migration Apoptosis	SCF, bFGF, HGF, KGF, NRG, NT-3, DKK1, sFRP2, Sema7a, CCN
Dermatofibroma	Hyperpigmentation Pink, grey, red, brown nodules	↗ Melanin synthesis ↗ Proliferation	SCF, HGF
Vitiligo	Hypopigmentation Depigmented, white patches	↘ Dendricity ↘ Proliferation	SCF, bFGF, DKK1 CNN, TGF-β

derived from keratinocytes is more likely to increase the melanin production and proliferation of melanocytes rather than soluble SCF derived from fibroblasts [56]. Fibroblasts are involved in pathological pigmentation, by an altered expression of various factors. Levels of HGF, SCF and KGF in dermis of café-au-lait macules and freckles are significantly higher than them in non-hyperpigmented dermis [57]. The tanning response to UV radiation exposure is mediated by a spectrum of locally produced cytokines and growth factors [58]. Mutations in genes encoding these regulators modify their expression and/or functionality, leading to altered signaling pathways, modified skin phenotypes, and development of benign lesions or tumors [59]. To better understand the dermal influence on skin pigmentation, this review focuses on some common pigmentary anomalies that involve fibroblasts-derived factors.

5.1. Melasma

Melasma is a common acquired hyperpigmentation disorder, occurred on forehead, cheeks and mandible. It affects appearance and has highly incidence in Latino, Asian and Dark-skin women. The number of melanocytes in melasma lesion is increasing however the activity of melanin synthesis enhanced. The pathogenesis and etiology of melasma have not been clearly identified, however, the previous researches identified the hormonal factors, family history, sun exposure and cosmetics as the four main triggering and aggravating factors for melasma development[60]. Some cytokines in epidermis such as SCF, PGE2, ET-1 are highly expressed in epidermis of melasma lesion[61]. The paracrine linkage between dermal fibroblasts and melanocytes also played an important role in the mechanism of hyperpigmentation in melasma. UV-repeated radiations stimulate directly or indirectly, through keratinocyte-derived cytokines, the secretion of soluble SCF by dermal fibroblasts. UVA radiations induce weaker effect on SCF secretion than those of UVB. Kang et al. found that SCF expression in the dermis of melasma lesion is significantly increased, its receptor c-kit on melanocytes is upregulated in dermis of melasma as well by immunohistochemical staining and RT-PCR [61]. In melasma, CCN proteins could be regulated by some factors related to pigmentary diseases such as FGF2, ET, estrogen and its receptors, progesterone and its receptors. Fibroblasts extracted from melasma express more NGF-β compared to fibroblasts from perilesional skin. Recently, researchers showed that expression of WIF-1 is significantly reduced in melasma lesion. Downregulation of WIF-1 in fibroblasts was reported to stimulate tyrosinase expression and melanosome transfer [62].

5.2. Solar lentigo

Solar lentigo (SL) is a common pigmentation disorder presented as aging spot on the exposure skin. It is characterized by hyperpigmented macules, and the number of the spots is related to the age and skin phototype. The histological characterization of SL is defined by a higher melanin deposition in the basal layer, elongated epidermal ridges and large melanosomal complexes. Differential gene-profiling analyses between SL and normal skin biopsies revealed that SL tissues are mainly composed of activated melanocytes [63]. Overexpression of HGF has been consistently proved in lentigo, and its receptor, c-MET, highly expressed in metastatic melanoma [64]. There are some fibroblast-derived paracrine factors such as HGF, KGF, SCF involved in SL lesion formation [65]. Immuno-staining analyses of some growth factors and secreted proteins in the upper dermis of SL biopsies strongly suggest that dermal fibroblasts contribute to functionally dysregulating the epidermal cells [66]. KGF synergy with IL-1 network described before effect was proved in solar lentigo as well [67]. KGF shows also efficiently ability to promote the production and secretion of SCF in keratinocytes [65].

5.3. Vitiligo

Vitiligo is a hypopigmentation disorder induced by dysfunction or deficiency of melanocytes. The etiology of vitiligo is still unclear. Most researches have concentrated on the abnormality of melanocytes and keratinocytes rather than the abnormality of fibroblasts. Low expression of SCF receptor c-kit in melanocyte at the edge of the lesion may indicate that downregulation of SCF/c-kit/MAPK signaling pathway contributes to dysfunction and loss of melanocytes [56]. It was reported that DKK1 secreted from fibroblast is highly expressed in vitiligo lesion and, β-catenin and PAR-2 expression in melanocyte is significantly lower in vitiligo lesion compared to non-lesion skin [68,69]. The dysregulation of Wnt signaling pathway in vitiligo lesion could prevent melanocyte differentiation. The occurrence of vitiligo could also be associated with some immune system disorders [70] such as thyroid disease, it has effectively been proved that DKK1 could increase the expression level of thyrotrophic embryonic factor and mitochondrial ribosomal proteins [71]. Furthermore, attachment of melanocytes to collagen IV is mediated through collagen-receptor DDR1 (Discoidin domain receptor 1) which is under the control of CCN3. The dysfunction of CCN3 and DDR1 interaction in vitiligo lesion causes weakly adhesion of melanocytes, and this process interacts with TGF-β and CCN2 [72].

5.4. Melanoma

Melanoma is the most serious type of human skin cancer that develops from melanocytes and occurs anywhere on the body especially in areas of the body that are exposed to direct sunlight. The main reason is caused by excessive UV exposure that damages DNA in melanocytes. Melanoma implicates not only malignant melanocytes, but also a heterogeneous mix of genetically stable non-cancer cells, including fibroblasts, endothelial and inflammatory cells. Infiltrated and surrounding stromal fibroblasts are recruited, perpetually activated through paracrine factors released from melanoma cells and transdifferentiated into cancer-associated fibroblasts (CAFs). One major source of CAFs in melanoma is resident normal skin fibroblasts. CAFs exhibit both morphological and functional differences compared to normal fibroblasts. They acquire properties of myofibroblasts, produce various growth factors, cytokines, and ECM proteins. Therefore CAFs participate in the growth and invasion of the tumor cells by promoting angiogenesis, inflammation and metastasis [73]. However, the exact mechanisms of how normal skin fibroblasts interact with malignant melanoma cells and subsequently transform to CAFs, are poorly understood [74]. Melanoma cells and dermal fibroblasts communicate throughout the tumorigenic process, including expression of numerous chemokines (IL-6, IL-8, CXCL1−3, CXCL8, CCL5, CCL2 . . .) and chemokine-receptors (CXCR4, CXCR2, CXCR3, CCR7 and CCR10 and CXCL1 . . .), and deregulation of signaling pathways (MAPK – PI3 K/AKT, Wnt/β-catenin) [75–77]. CAFs secretion of HGF results in activation of the c-MET receptor and signaling pathways [78]. Expression of SCF, bFGF and KGF is involved in melanoma genesis [79,80]. UV exposure induces upregulation of FAP-α in fibroblasts, and contributes to migration and invasion of melanoma cells [52]. HGF receptor, c-MET, highly expressed in metastatic melanoma pathway maintains the melanocyte survival by suppressing the pro-apoptotic Bad protein and increasing the anti-apoptotic Bcl-xl [38]. Nuclear Factor-kappa β (NF-kB), a transcription factor involved in the immune response, has been shown to be upregulated in melanoma through deregulations in upstream signaling pathways such as Ras/Raf, PI3 K/Akt. Therefore, targeting stromal fibroblasts and inhibiting stromal NF-kB signaling could be a possible treatment for melanoma [35,50,81,82]. NT-3 mediates cell invasion and ECM degradation in metastatic melanoma [81]. Additionally, development and progression of melanoma are associated with deregulation of Wnt signaling and loss of DKK-1 secreted by fibroblasts [83–85]. DKK-1 is known to be regulated by the canonical Wnt pathway. In normal melanocytes, Wnt pathway is activated by secretion of Wnt3a. However, in malignant melanocytes, Wnt5a which is an inhibitor of DKK-1, is expressed. It is also suggested that phenotypic changes of melanocytes in melanoma tumor are associated with senescence, particularly in the dermal compartment. The secretion of factors from senescent fibroblasts, such as MMP-3, IL-6, TGF-β, alters epithelial differentiation, promotes endothelial cell motility and stimulates cancer cell growth and tumorigenesis [86]. In addition, senescent fibroblasts accumulate during aging. Secreted sFRP of aged dermal fibroblasts drive melanoma promoting both angiogenesis and metastasis [87]. Besides, loss of Sema7a receptor Plexin C1 may induce melanoma invasion and metastasis, and therefore Plexin C1 is known as a potential tumor suppressor for melanoma progression [88]. Downregulation of CCN3 in melanoma cells contributes to their invasive phenotype [89].

5.5. Dermatofibroma

Dermatofibroma (DF), also known as fibrous histiocytoma, is a benign common cutaneous nodule of fibroblast-like cells with unknown etiology. Histologically, DF lesion is characterized by a hyperpigmentation in the overlying epidermis with acanthosis and with an increased number of melanocytes. Proliferating fibroblast-like cells and histiocytes accumulate in the dermis and are surrounded by mature collagen and by increased capillaries. They secrete elevated gene and protein levels of SCF and HGF cytokines and stimulate melanocytes located in the adjacent epidermis, which results in the hyperpigmentation of the overlying skin[50]. The altered expression of SCF and HGF in DF lesions can be associated with the tumor cell proliferation and induction of DF. SCF or HGF derived from the fibroblastic tumor may function as a mitogen for melanocytes [90]. SCF is also known as mast cell growth factor and this explains why accumulation and degranulation of mast cells are observed with melanocyte activation in DF lesions. However, further studies are required to identify the factors that stimulate exclusively in abundance the secretion of SCF and HGF.

6. Conclusion

Cutaneous pigmentation is regulated by melanogenic factors, locally synthesized in the skin by both keratinocytes and fibroblasts, or produced by distant tissues and transported to the skin by the circulation. Many of those factors regulate constitutive and induced pigmentation. In this review, the contribution of dermal fibroblasts to the regulation of melanocyte activities is demonstrated. Fibroblasts interact with melanocytes directly and indirectly through keratinocytes. They release numerous biochemical factors that modulate the pigmented status of melanocytes by activating signaling cascades, gene expression and enzyme activity. *Levels* of *fibroblast-derived* melanogenic paracrine *mediators depend on intrinsic and extrinsic factors such as skin type, genetic, sun exposition.* Increased researches on the importance role of fibroblasts in melanocyte function under physiological or pathological conditions provide theory evidences for treatment of pigmentary disorders.

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Conflicts of interest

The authors have no conflict of interest to declare.

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