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Dermal fibroblast in cutaneous development and healing

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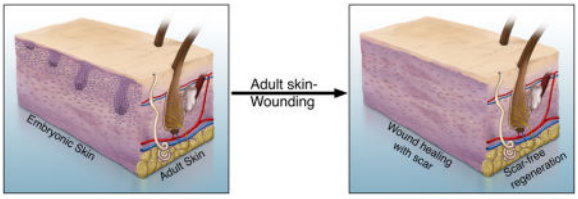
Abstract

The skin is the largest organ of the body and is composed of two layers: the overlying epidermis and the underlying dermis. The dermal fibroblasts originate from distinct locations in the embryo and contain the positional identity and patterning information in the skin. The dermal fibroblast progenitors differentiate into various cell types that are fated to perform specific functions such as hair follicle initiation and scar formation during wound healing. Recent studies have revealed the heterogeneity and plasticity of dermal fibroblasts within skin, which has implications for skin disease and tissue engineering. The objective of this review is to frame our current understanding and provide new insights on the origin and differentiation of dermal fibroblasts and their function during cutaneous development and healing.

Graphical Abstract



Introduction

The skin has served as an excellent model system to understand the complex interplay of different cells types and molecular signaling pathways during development and homeostasis [1–9]. Skin organ homeostasis is achieved through constant crosstalk between the major components: dermal fibroblasts, keratinocytes, immune cells, nerves, and intradermal adipocytes [10–13]. The epidermis gives rise to the hair and glands and contributes to thermoregulation and barrier formation [1]. The dermis provides the structure, strength and flexibility to the skin, and houses other structures such as hair, glands, vessels, and nerves. The main resident cell type of the dermis is the dermal fibroblast, which produces the extracellular matrix (ECM) and contribute to hair follicle initiation and cycling [10,14,15]. Early embryonic dermal fibroblast progenitors can potentially differentiate into several cell types such as upper papillary fibroblasts (PF), lower reticular fibroblasts (RF), dermal condensate/dermal papilla (DP), and intradermal adipocytes/dermal white adipose tissue

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(DWAT) [16]. The papillary dermis plays an instructive role for the overlying epidermis in appendage formation [17–21]. The adult epidermis and dermis generally lack the capacity to regenerate skin completely after wounding with the exception of the African spiny mouse which has scar-free healing. Gaining deeper insights into dermal fibroblast development can take us one step closer to developing fibroblast-directed therapies for scar-free healing. Here, we will primarily highlight the origin of dermal fibroblasts; genesis of their derivatives; heterogeneity among dermal populations, and their role in wound healing.

Origin of dermal fibroblasts

Cell fate-mapping analysis using a variety of techniques in the chick and mouse embryo reveals similarities and differences in the origin of dermal fibroblasts. In the avian and mouse embryo, dorsal dermal fibroblast progenitors originate from the somite [22–24]. The ventral and flank trunk dermis, as well as limb dermis, is derived from the lateral plate mesoderm and migrates beneath the ectoderm [25–27] (Figure 1). In birds, craniofacial dermis arises entirely from cranial neural crest that migrates extensively from the dorsal neural tube to populate the skin of the head and face [28,29]. In contrast, mammalian craniofacial dermis has a dual embryonic origin of cranial neural crest and cephalic mesoderm [28,30,31]. These lineage analysis experiments in both mouse and chick reveal that embryonic dermal fibroblasts originate from different parts of the embryo and populate the skin closest to their origin.

Emergence of dorsal, ventral, and craniofacial dermal fibroblast progenitors

Our understanding of emergence and early migration of dermal fibroblast precursors and specified progenitors comes from extensive studies in avian models. It is of general consensus that these mechanisms are evolutionarily conserved in other vertebrate models as well.

The chick and mouse dorsal trunk dermal fibroblasts originate from the dermomyotme (DM) of somites [22,32,33]. The dermal fibroblast precursors delaminate from the dorsal portion of the DM and migrate short distances to populate the fibrous lattice of subectodermal extracellular space in response to signals from the neural tube and ectoderm [34]. Preceding migration, the dorsal DM cells undergo epithelial to mesenchymal transition (EMT) and express *Wnt11* [34,35]. *Wnt11* silencing in the chick DM hinders EMT and migration of dorsal dermal precursors [36]. Likewise, the *Wnt11*$^{-/-}$ mutant mouse has reduced dermal volume and hair follicle density in the dermis directly above the neural tube [36]. The mechanism through which *Wnt11* promotes the movement of dermal fibroblast precursors is unknown. In both chick and mouse embryos, cells delaminate from the dorsal somatopleure of the lateral plate mesoderm (LPM) and give rise to the flank, ventral trunk, and limb dermis [25,26,37]. Between E9.5 and E12.5 in the mouse, WNT/β-CATENIN signaling is required for survival of the ventral dermal precursors and their migration to the midline [25].

The mammalian facial dermis is derived from cranial neural crest cells (cNCCs) and the cranial dermis is derived predominantly from the paraxial/cephalic mesoderm [28,30,38]

(Figure 1). The avian craniofacial dermis is thought to be derived entirely from cNCC [29]. Between E8.5 and E9.5 in the mouse, forebrain and hindbrain cNCCs migrate extensively from the neural plate border to the branchial arches and frontonasal mass [39,40]. cNCCs under the ectoderm become the dermal precursors of the face and anterior head (Figure 1). Both attractive and repulsive cues, specifically ephrins and semaphorins, govern the cNCC migratory path [41,42]. cNCC proliferation and survival during migration is regulated by Platelet derived growth factor receptor (PDGFR)-αlpha signaling through PI3/Akt signaling [43]. The forebrain and midbrain cNCC migrate to the anterior supraorbital arch (SOA) region above the eye by E10.5 and become dermal fibroblast precursors for the forehead skin [28,31]. The cephalic mesoderm cells migrate to the posterior SOA by E10.5 (Figure 1) and become dermal fibroblast precursors for most of the cranial skin. From E10.5, the specified cranial dermal fibroblast progenitors expand apically from the SOA to fill the cranial region [28,30,31].

The signals and mechanism of cellular movements underlying the expansion of dorsal, ventral, and cranial dermal progenitors are largely unknown. The next frontier is to understand how intrinsic genetic instructions and extrinsic spatial information guide large scale cellular movements to create the dermis. These results along with more detailed fate maps will be informative for understanding the etiology of congenital dermal hypoplasias such as Setleis syndrome, Goltz syndrome, and Aplasia cutis congenita [44–46].

Dermal fibroblasts cell fate selection

During cell fate selection between E10.5–12.5, WNT/β-CATENINsignaling is the earliest signaling pathway in the dermal fibroblast progenitors, and it is instructive for dermal fibroblast cell fate (Figure 2) [4,22,25,31]. Throughout the embryo, the early dermal fibroblast progenitors in the sub-ectodermal regions from E10.5 are WNT signaling responsive and express nuclear β-catenin [4,22,25,31]. Ectodermal WNTS are necessary for dermal WNT signaling responsiveness. Conditional deletion of cranial or dorsal ectoderm *Wntless*, a cargo protein required for all WNT ligand secretion, leads to loss of early dermal lineage markers in the cranial and dorsal regions, respectively [15,47]. Conditional ablation of β-catenin in craniofacial and LPM dermal progenitors starting at E9.5 leads to conversion of dermal lineages to cartilage [25,31]. Conversely, sustained expression of stabilized β-catenin leads to expansion of dermal progenitors suggesting it is sufficient to elicit dermal fate [15,25,31]. Thus, WNT/β-CATENIN signaling is an instructive cue for specifying dermal fibroblast cell fate throughout the embryo and inhibits alternative cell fates by a yet unknown mechanism.

During dermal fibroblast cell fate selection, WNT/β-CATENIN signaling regulates several of the key known transcription factors such as *Twist1, Twist2/Dermo1, Msx1/2*, and *Engrailed1* in the dermal progenitors [48] (Table 1). Gene deletion of these transcription factors individually does not lead to change in cell fate, suggesting functional redundancy [49–51]. Current data suggest that the *Twist* family of transcription factors are promising effectors of β-catenin signaling in dermal fibroblast cell fate selection in the entire embryo [34,52,53]. First, *Twist1* and *Twist2* are some of earliest markers of chick and mouse dermal fibroblast progenitors and are also direct transcriptional targets of β-catenin [22,25,31,34,54]. Second, TWIST1/2 proteins function to inhibit other mesoderm related lineages such as

muscle, bone, and cartilage [55–58]. Third, *Twist1*$^{+/-}$; *Twist2*$^{+/-}$ compound heterozygotes and *Twist2*$^{-/-}$ mice have thinner dermis and sparse hair in perinatal skin [44,59], suggesting functional redundancy between the family members during dermal fibroblast development. Fourth, TWIST1 overexpression in epithelial cells leads to EMT due to loss E-cadherin mediated cell-cell adhesion, increase in motility, change in morphology, and increase in expression of fibroblast proteins, such as fibronectin and vimentin [60]. Future conditional genetic experiments designed to overcome the functional redundancy of TWIST1 and TWIST2 will be needed to determine their precise role in dermal fibroblast development.

Does positional memory confer regional identity in embryonic and adult dermal fibroblasts?

Though all dermal fibroblasts appear morphologically similar, they have distinct positional identity and function at different anatomical locations [14,17,61–63]. Skin patterning with appendages and pigmentation varies regionally in the dorsum, ventrum, face, and cranium. Several studies show that the embryonic origin of fibroblast confers positional identity and memory for skin patterning and function. Heterotopic recombination experiments across anatomical regions or between species reveal that dermal fibroblasts can reprogram the epidermis [17,21]. For instance, scale-forming dermis recombined with feather-forming epidermis gives rise to scales in recombinant skin [17]. Similarly, quail cranial dermis promotes quail feather formation in a duck embryo [21]. Conversely, studies reprogramming epidermal structures between follicular, interfollicular, and glandular fates also report accompanied cellular identity and functional changes in the dermal compartment. Collins et al. [64] found expression of constitutively active β-catenin in the adult epidermis leads to conversion of adult dermis into neonatal dermal fibroblast identity and function. Overexpression of Noggin, a Bone Morphogenetic Protein (BMP) inhibitor, or ablation of *Bmpr1a* in the ventral foot pad epidermis leads to conversion of eccrine sweat glands to hair follicles that recruit dermal fibroblasts to form ectopic dermal papilla [65].

Recently, Rinkevich et al., performed a classical tissue recombination experiment to demonstrate cell intrinsic function based on embryonic origin [63]. In the adult mouse, oral dermis and dorsal dermis were reciprocally-transplanted in the dorsal skin and oral cavity, respectively. Wounding of the dorsal dermal graft in the oral cavity lead to scar formation which is absent in the oral dermal graft in dorsal wild type skin. This experiment demonstrates that scar forming ability is intrinsic and independent of the host microenvironment. The result can be partly explained by the presence of cellular positional memory that can promote specific gene expression patterns and regulate function [61,66].

The positional identity of dermal fibroblasts in humans is regulated by a combinatorial code of *Hox* genes established in embryonic development and is stably maintained into adulthood and *in vitro* [61,62]. However, it is not known how the different *Hox* genes regulate dermal fibroblast function of diverse skin patterning. Future studies will need to investigate whether the genes conferring site-specific positional identity also provide inductive cues to pattern the epidermis *in vivo*. Taken together, these studies show the intrinsic positional identity in the dermal fibroblasts and their ability to reprogram the epidermis [17,21,63]. They also reveal

that dermal fibroblast identity and function is plastic and can also be reprogrammed [64], thereby demonstrating active cross-talk between the two layers in embryonic and adult skin.

Dermal fibroblast progenitor differentiation into hair inducing and matrix forming fibroblasts, and perhaps intradermal fat

Starting at E14.5, the specified dermal progenitor further differentiates into its derivatives (Figure 2) [16]. As early as E12.5, the dermal progenitors express pan-fibroblast markers, *PDGFR-alpha* and *Engrailed1 (En1)* [16,22,67]. Around E14.5, these dermal progenitors give rise to papillary and reticular dermal lineages which are distinct in their gene expression pattern with varying functions [16]. The papillary dermal progenitors gives rise to papillary dermal fibroblasts (PF) and dermal papilla (DP), and the reticular dermal fibroblast progenitors gives rise to reticular fibroblasts (RF) and dermal white adipose tissue (DWAT). PF and DP play a crucial role in hair follicle morphogenesis and cycling [68,6915]. RF secrete dense collagen fibers that provide structural integrity and strength to the skin. DWAT, also called intradermal fat, is a recently defined cell type that is significantly different from subcutaneous fat in terms of developmental origin and contributes to the skin barrier [70,71]. The underlying signaling mechanism(s) for differentiation of papillary and reticular dermal fibroblast lineages are yet unidentified. However, we predict WNT signaling activity levels differ and contribute to the differentiation of the papillary and reticular lineages. From E12 to E14.5, the epidermis expresses canonical WNTs and the upper dermal lineage is Wnt-responsive to the ectodermal WNTs [4,15,72]. This in turn supports our putative hypothesis that dermal layers are divided into the top WNT^{high} and deeper WNT^{low} regions leading to its further differentiation. This hypothesis remains to be rigorously tested in available mesenchymal β-catenin and *Wntless* mutants [15,22,72].

During embryonic development, the PF cells have a unique capacity to support hair follicle initiation, but the nature of the primary dermal signal is still elusive [73,74]. Classical heterotopic tissue recombination experiments led to the idea that an inductive dermal signal is necessary for hair follicle initiation [75–77]. Four decades after this concept was defined, the inductive dermal signal remains elusive [10]. The primary dermal signal is likely regulated by WNT/β-CATENIN signaling. Ablation of WNT/β-CATENIN signaling in specified dermal fibroblasts prior to epidermal placode formation leads to absence of placodes and hair follicles [15]. The downstream effector(s) of the primary dermal WNT/β-CATENIN signaling is unknown and it may be either molecular or mechanical. The mechanical properties of tissue/cells can regulate cell-cycle, stem cell differentiation, disease progression *etc*. [78–80]. In the chick embryo, the formation of high cell density dermis is thought to be required for feather placode initiation [17]. And varying the density of dermal fibroblasts in tissue recombination experiments *in vitro* revealed that a critical density of dermal fibroblasts was necessary for self-organization of placode formation [73]. Recently, Shyer et al. show that tissue symmetry is broken by mechanosensation of β-catenin in the dermal progenitors and is critical for initiating the follicle structure and molecular program in the avian skin [81]. It remains to be investigated if mammalian dermal fibroblast progenitors form fibroblast microaggregates in the future hair follicle placode fields which then become stable and mechanically signal to the epithelium to form a placode [73,81]. Technological improvements

in live cell imaging of the dermal layer should aid in observing small scale cellular movements and cellular density changes prior to placode formation.

After the epidermal placodes form, clustering of underlying papillary dermal fibroblasts occurs to form the dermal condensate (Figure 3) [73,74,82]. Subsequent cross-talk between the epidermal placode and the dermal condensate promotes cutaneous appendage down growth [17]. The dermal condensate cells are precursors of the specialized mammalian fibroblasts called the dermal papillae (DP) that reside at the base of the adult hair follicle (Figure. 3) [74,83]. Studies in chick embryonic skin suggest that dermal condensates most likely form upon dermal fibroblast rearrangement and migration in response to signals from the ectoderm. During the initial stages of formation, there is plasticity in cell identity of the interfolliclular dermal fibroblasts and fibroblasts in the dermal condensate [73]. Dermal condensate formation is dependent on cell migration and cell adhesion, but not cell proliferation [82,84,85]. The *Scaleless* chick mutant shows that placodal signals are required for dermal condensate formation from the papillary dense dermis [86]. A variety of secreted molecules are expressed in the placode and can serve as either activators (Shh, FGF, TGFβ2, WNTs, Ectodysplasin) or inhibitors (BMPs) in the placode of the chick and mouse skin [83,87]. The target genes of these factors are expressed in dense dermis and later upregulated in the condensate (nuclear β-CATENIN, LEF1) or first appear in the dermal condensate (BMP4/7, NOGGIN, FGF7/10, PDGF-alpha). Signaling factors such as SHH, BMP and TGF-β are shown to be dispensable for hair initiation and dermal condensate formation [5,88,89]. Currently, we lack genetic tools to study the emergence of dermal condensate formation in a short interval after placode formation. Thus, questions about how dermal fibroblasts initiate hair and differentiate to dermal condensate fate remain unanswered. Use of single cell RNA-seq could be used to tease out the transcriptional signatures of these rapidly differentiating cell types.

The DWAT layer in the skin is distinct from the subcutaneous fat layer and can contribute to the skin barrier, wound healing, and hair follicle cycling [11,90]. DWAT, is derived from PDGFRα expressing mesenchymal lineage but its precise origin is unknown [67] (Figure 2). The reticular dermal lineage expresses DLK1 from E16.5 [16]. The preadipocytes at postnatal (P) day2 in the skin express SCA1 and a subset express DLK1. These data suggest that DWAT is derived from the reticular dermal lineage. However, additional *in vivo* genetic lineage tracing would greatly strengthen our current understanding of the origin of DWAT which has implications for cutaneous homeostasis, healing, and disease. Recently, Plikus *et. al.* showed *alpha-Sma-Cre* lineage-marked cells in a wound bed can give rise to DWAT fate [91]. The identity of *alpha-Sma-Cre* lineage marked cells may not be restricted to only myofibroblast cells. The signals required for specifying DWAT fate are also unknown. Sustained activation of dermal WNT/β-CATENIN signaling at E16.5 using the *HoxB6CreER* or *Dlk1CreER* lowers the intradermal adipocyte numbers and enhances reticular fibroblast proliferation and ECM production, thereby resulting in dermal fibrosis [92,93]. DWAT, unlike other adipose layers, dynamically changes in size during hair cycling and perturbing its ability to regenerate results in cycling defects [90]. Thus, there is cross-talk between DWAT, dermal fibroblasts, and follicular cells and it would be interesting to identify other homeostatic mechanisms regulated by DWAT.

Dermal fibroblasts in scar forming and scar-free wound healing

Dermal fibroblasts perform a crucial task in wound healing by populating the wound site to produce ECM which forms a scar [16,94]. Selectively eliminating *En1* lineage dermal fibroblasts in adult skin leads to delay in wound closure, showing the presence of an intrinsic fibrogenic lineage that is determined during embryonic stages [63]. RFs selectively populate wound beds immediately after wounding in comparison to the PFs [16]. RFs are naturally selected for the task because of their intrinsic ability to produce thick and organized collagen in comparison to poorly organized and loosely packed ECM of the PFs [95,96]. Taken together, these data suggest that the dermal fibroblasts, particularly RFs are important for migrating into and healing the wound. Fibroblast migration to the wound is regulated by inflammatory mediators such as C5a, fibronectin, PDGF, fibroblast growth factor (FGF), and TGF-beta [13,97–99]. Recent evidence suggests that DWAT is also necessary. Either absence of mature adipocytes (A-ZIP/F1 transgenic mice [100]) in the skin or inhibition of adipogenesis stunts fibroblast recruitment to the wound site leading to delay in wound closure [11].

The normal wound healing program results in a scar which is different from normal skin aesthetically, functionally, and morphologically. The scar is composed of poorly reconstituted collagen in dense parallel bundles which affects the homeostatic mechanisms in and around the site. The scar lacks hair, glands, and touch and pressure sensors of the skin (See Graphical Abstract). Thus, it is clinically relevant to understand ways to regenerate scar-free skin.

Wound-induced hair follicle neogenesis (WIHN): partial scar-free wound healing model

Historically, it was presumed that mammals fail to regenerate cutaneous appendages in a wound site, but several reports in the 1940s reported WIHN in rabbits and rats [101]. Only in 2007, Ito et al showed hair follicles in the center of large excisional mouse cutaneous wounds occur *de novo* by recapitulating embryonic hair follicle formation [102]. In a recent landmark study, Plikus et al., exploited fibroblast plasticity to regeneration of the intradermal adipocytes in WIHN. They found wound myofibroblast can be reprogrammed to intradermal adipocytes in response to BMPs secreted by *de novo* hair follicles during WIHN. Thus, WIHN provides a model system to identify the mechanisms regulating hair follicle neogenesis in adult skin and identify cell types to manipulate for complete skin regeneration [91]. Both dermal and epidermal WNT/β-CATENIN signaling are crucial in embryonic hair follicle initiation [15,72,102–104]. Similarly, either ablation or overexpression of epidermal WNTs in adult mice resulted in absent or enhanced WIHN respectively [102,105]. WNT signaling in dermal fibroblasts is active in late wound stages and is induced by FGF9 from γδ T-cells that populate the wound site [12]. Based on these observations, it is tempting to speculate that dermal WNT signaling is necessary for WIHN, however conditional ablation of dermal β-catenin lead to enhanced WIHN[106] These results raise new questions: (i) What are the downstream effectors of dermal WNT/β-CATENIN signaling regulating WIHN? (ii) How are they similar and different from β-catenin effectors in embryonic hair follicle initiation? (iii) Is there a redundant mechanism for WIHN that is WNT-independent?

Scar-free wound healing and skin regeneration

In the effort to rejuvenate and engineer skin as an organ, mechanisms of scar-free wound healing in adult skin need to be fully understood. A cutaneous wound can regenerate without scar in specific contexts [107]. The human embryo is capable of scar-free skin wound healing, but this ability is lost around the third trimester of gestation [108]. The difference can be partly explained by the more mature innate immune system response and subsequent gene expression changes in the wound bed of adult skin. [109]. Excisional wounds in a neonatal *PU.1* null mouse that lacks macrophages and functional neutrophils exhibit scar-less healing as seen in embryos [110]. Ablation of macrophages recruited during the initial inflammatory phase of wounds leads to reduction in scar formation [111,112]. Similarly, embryonic day 18 mouse wounds lacking mast cells heal with reduced scarring [113]. Furthermore, multiple studies have demonstrated that the number of mast cells and dermal dendritic cells that express FXIIIa are significantly more in keloids and hypertrophic scars suggesting that they may play a causative role in scarring [111,114].

In embryonic mice, scar-free wounds express less TGF-beta1 than adult wounds and the ratio of TGF-beta1/TGF-beta3 is higher in a scarring wound [115,116]. Consistently, oral cavity wounds that regenerate without scarring in adults exhibit lower immune infiltrate and TGF-beta1/TGF-beta3 ratio compared to external cutaneous wounds. [117,118]. Therefore, a recombinant human TGF-beta3, Avotermin, has been escalated to clinical trials in order to prevent scarring post surgeries. It was successful at reducing wound induced scarring in phase I/II studies and improving efficacy at lower dose remains to to be developed [119]. These findings suggest that the composition of various TGF-betas isoforms regulate scarring and many other drugs modulating this pathway are under clinical trials in fibrotic and wound healing setting [120]. TGF-betas are secreted by immune cells and platelets during early stages of wound healing and later by fibroblasts [121,122]. Furthermore, the ratio of COLLAGEN Type 3 to COLLAGEN Type 1 secreted by dermal fibroblasts is higher in fetal wounds than postnatal wounds [123,124]. Together, these data suggest if gene expression changes in adult dermal fibroblasts can be altered to resemble early stage embryos, we might achieve scar-less wound healing.

Generally, adult mammals lack the ability to regenerate skin fully, however an upcoming mammalian model, *Acomys,* the African spiny mouse can regenerate skin from wounds as large as 60% of its body surface complete with follicles, glands and DWAT [125] (See Graphical Abstract). Wounded skin of *Acomys* exhibit modest inflammation to wounding and the ECM profile resembles early stage human fetal skin with higher levels of COLLAGENS 3α1, 5α1, 5α2 [126]. There is modest upregulation of CXCL cytokines in *Acomys* compared to a significant increase in adult murine wounds. *Acomys* dermal fibroblasts secrete matrix metalloproteinases (MMP) and other enzymes that catabolize collagen, leading to faster ECM remodeling and enhanced cell migration [126,127]. Similarly the expression of MMPs correlate with the ability of skin regeneration in fetal rats [128]. Alpha-SMA expressing myofibroblasts that are implicated in scar forming ECM are absent in *Acomys* ear skin wounds in comparison to mice [125]. All these factors together may contribute to scar-free wound healing in *Acomys*. In essence, *Acomys* skin retains the early embryonic wounding response and achieves scar-free healing throughout its lifetime. By and

large, it can be hypothesized that a treatment targeted towards chemokine and TGF-beta1 inhibition, along with increased ECM degradation, is the key to scar-free skin. Though *Acomys* provides crucial gene candidates, the upstream regulators of the observed effects are unknown. Deeper understanding of skin regeneration in *Acomys* will move us closer towards developing scar-free wound healing remedies in humans.

Concluding remarks

Dermal fibroblasts serve as a model cell type in understanding various regulatory processes in development and healing. Numerous new insights about them are covered in this review, but there are many more questions that need to be addressed in the future: (i) Though early dermal progenitors give rise to papillary and reticular dermis, the signaling pathways that specify these derivatives are not known. Because multiple cell types express PDGFR-alpha, more accurate lineage maps are needed to understand the differentiation program of dermal derivatives such as DWAT. (ii) We need to identify signals underlying small and large scale cellular movement of dermal fibroblast progenitors during migration and preceding hair follicle initiation. (iii) The HOX code can impart positional memory in adult human fibroblasts, but its role in guiding skin patterning *in vivo* remains to be tested. (iv) The nature of the primary inductive signal from the dermis to epidermis prior to placode formation needs further investigation. (v) A deeper understanding of the regulatory mechanisms and downstream signals involved in scar-free wound healing models will be needed for treating scars in humans.

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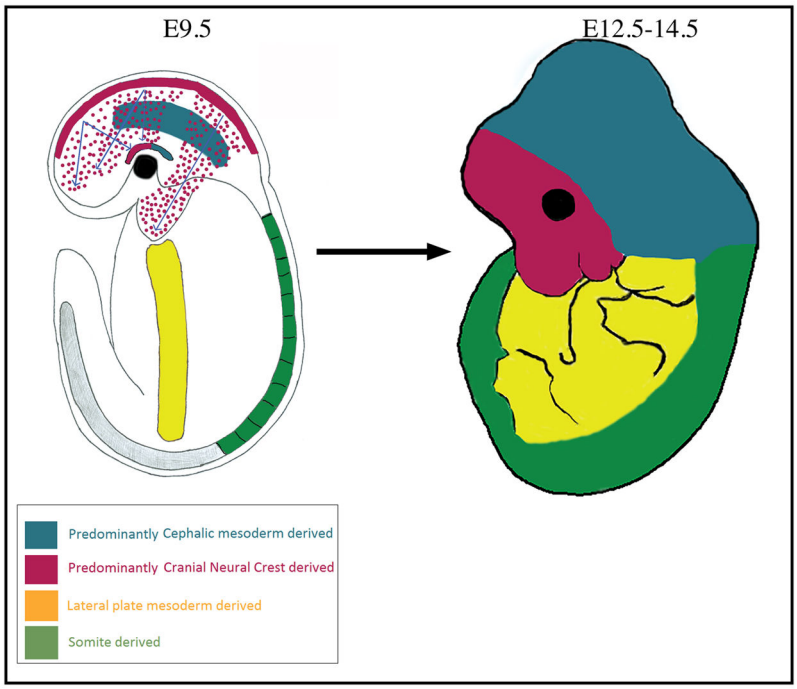

Figure 1.

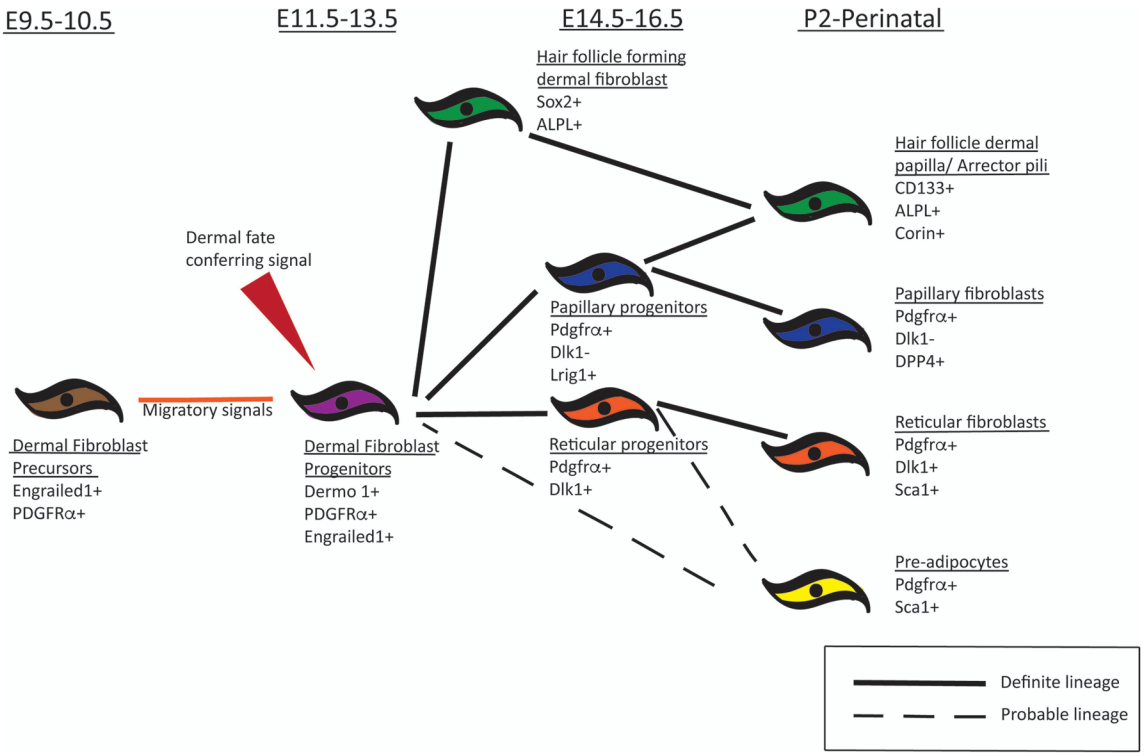

Figure 2.

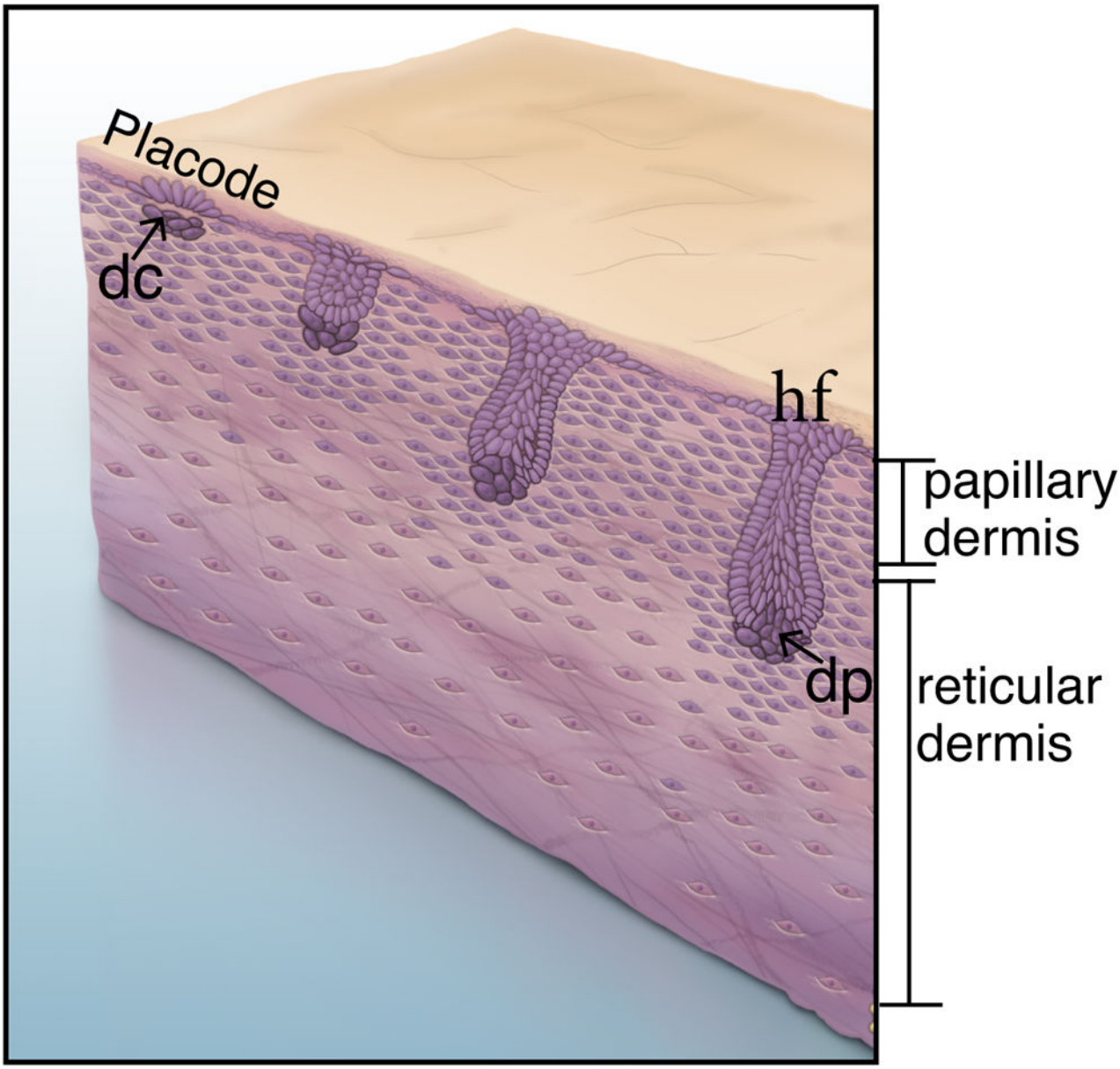

Figure 3.

Table 1

Transcriptional factors in dermal fibroblast precursors and progenitors

Genes	Spatiotemporal expression in skin	Phenotype (defects in dermal fibroblast, defects in hair/DC/DP)	Reference
Msx1/ Msx2	Mesenchymal cells underlying the ectoderm of the back of the trunk from E9.5-E13.5	The number of hair follicles is reduced to one-third that of wild type, a failure of mammary epithelial invagination, development arrests at the lamina or early bud stages in *Msx1−/−, Msx2−/−* mutant embryos	(Houzelstein et al., 2000;Satokata et al., 2000; Satokata et al., 1994)
Prx1/Prx2	Expression in the somites was confined primarily to the dorsal dermamyotome	No obvious cutaneous abnormality reported	(Cserjesi et al., 1992; ten Berge et al., 1998; Bergwerff et al., 2000)
Sim1	*Sim1* is expressed in medial dermamyotome from E9.5	No obvious cutaneous abnormality reported	(Guillemot et al., 1993)
Twist1/ Twist2	*Twist1/2* are expressed in embryonic mesoderm starting at E9.5	*Twist-2−/−* mice also showed notable cutaneous abnormalities; with dramatically thin skin and sparse hair. No obvious cutaneous abnormality reported in *Twist1* mutants.	(Li et al., 1995; Chen & Behringer, 1995; Sosic et al., 2003)
Engrailed1 (En1)	*En1* is expressed in dorsal dermamyotome, lateral plate mesenchyme, and cNCC from E9.5	No obvious cutaneous abnormality reported	(Atit et al., 2006; Ohtola et al., 2008; Tran et al., 2010; Augustine et al., 1995)