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Review

Mesenchymal–epithelial interactions during hair follicle morphogenesis and cycling

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ABSTRACT

Embryonic hair follicle induction and formation are regulated by mesenchymal–epithelial interactions between specialized dermal cells and epidermal stem cells that switch to a hair fate. Similarly, during postnatal hair growth, communication between mesenchymal dermal papilla cells and surrounding epithelial matrix cells coordinates hair shaft production. Adult hair follicle regeneration in the hair cycle again is thought to be controlled by activating signals originating from the mesenchymal compartment and acting on hair follicle stem cells. Although many signaling pathways are implicated in hair follicle formation and growth, the precise nature, timing, and intersection of these inductive and regulatory signals remains elusive. The goal of this review is to summarize our current understanding and to discuss recent new insights into mesenchymal–epithelial interactions during hair follicle morphogenesis and cycling.

Contents

1. Introduction

A hair follicle is the primary unit that produces a single outgrowing visible hair shaft. In mice, multiple hairs are induced all over the body and patterned to form rows of eyelashes, discrete whiskers, or densely clustered pelage hairs. All fulfill a wide range

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of functions, including control of body temperature, providing physical protection, relaying sensory and tactile input, and serving decorative purposes for social interactions. At least eight different major hair types can be distinguished in mice [1], and the hair coat alone contains four separate hair subtypes [2].

All hair follicles have the same basic arrangement, with epithelial progenitor cells at the base giving rise to multiple intermediary cell lineages that form the hair shaft and its guiding channel. Epithelial progenitors themselves surround a core cluster of mesenchymal cells, the dermal papilla (DP), which is thought to provide signals to coordinate hair growth [3]. The exchange of molecular cues between epithelial and mesenchymal compartments begins during embryogenesis, when hair follicles are first formed [4]. Remarkably, many of the fundamental signaling programs required for hair morphogenesis are evolutionarily conserved across species with different types of skin appendages, such as feathers and scales [5]. Furthermore, parallels exist between the mechanisms driving hair, tooth and mammary gland formation, all of which require mesenchymal–epithelial interactions [6]. After initial hair follicle formation and a prolonged period of growth, follicles undergo cycles of destruction and regeneration throughout life [7]. For new hair re-growth, signal exchange between DP cells and stem/progenitor cells is thought to occur in a process that is reminiscent of embryonic hair follicle formation [8]. Many diverse developmental programs require coordinated mesenchymal–epithelial interactions for completion, and studies of hair growth provide an exquisite system in which to study the complexities of this universally important process.

Numerous methods have been used to characterize the interplay of signals exchanged between the mesenchymal and epithelial components during embryonic follicle initiation, postnatal growth and adult regeneration. An early approach involved tissue recombination experiments, which determined that dermal signals initiate follicle formation [9]. Subsequent microdissection and transplantation experiments revealed the inductive and nurturing role of specialized DP cells [10] and localized multipotent epithelial stem cells to the follicle bulge [11]. The identification of putative ligands and receptors involved in mesenchymal–epithelial interactions came from tissue stainings performed since the 1990s, and more recently from studies systematically assessing gene expression with the help of genetic fluorescent reporter tools [12–15]. The functional relevance of many ligands has been explored by bead implantation experiments, complete gene knockout mice and spontaneous mouse mutants [16]. Most recently, compartment-specific gene ablation [17] and transgenic overexpression in the epidermis [18] and bulge stem cells [19] of candidate ligands and receptors yielded many insights into the requirement and timing of several signaling pathways for hair morphogenesis. In this review, we will highlight the basic concepts of hair follicle development, discuss our current understanding of the signal exchange during this process, and review recent new insights into the mesenchymal–epithelial interactions driving follicle induction, growth and regeneration.

2. Overview of hair follicle development, growth and regeneration

2.1. Hair follicle formation

Classically, the initiation of hair follicle morphogenesis is described in terms of an ordered series of mesenchymal–epithelial interactions: a “first signal” emanating from the dermis acts on an unspecified epidermis, and the formation of morphologically recognizable hair placodes follows next [4,8]. Several studies have proposed that mechanisms of lateral inhibition, mediated by diffusible signals that act within the epidermal compartment, coordinate the even spacing of these placodes [20–22]. As development progresses, stabilized placodes signal to underlying dermal cells, prompting the formation of dermal condensates or clusters of DP precursor cells. Finally, these condensates are believed to signal back to the epithelial compartment to stimulate proliferation and downgrowth of hair germs [4]. Hair follicle stem cells arise from epidermal progenitors early on [23] but remain located in the upper portion of the follicle while supplying rapidly dividing cells at the tip that allow further downgrowth of the hair peg. As the epithelial component of the nascent follicle extends deep into the skin, DP precursor cells remain at the leading edge and are eventually engulfed. The dermal component of the mature hair follicle consists of these DP cells, which remain in the bulb region, and an adjoining connective tissue sheath that encircles the follicle in its entirety [4].

The first epithelial placodes appear at embryonic day E14.5, and eventually develop into primary guard hair follicles. These unique hairs comprise only 1–5% of the adult mouse coat, and are distinguished by their large follicle size and longer shaft length. Primary placodes have already progressed to form prominent downgrowths by E16.5, when a second wave of placode formation initiates. Secondary placodes appear in an even distribution between established guard follicles and give rise to awl and auchene hairs. These contribute to twenty percent of the final adult coat, with smaller follicles and shorter shaft lengths compared to primary guard hairs. A third and final wave of placode formation begins at E18.5, giving rise to zig-zag hairs that represent the vast majority of the adult coat [2,24].

2.2. Hair growth phase

After initial hair follicle downgrowth, the DP is completely encased by the lowest part of the hair bulb, although it remains separated from the epithelial compartment by an enveloping basement membrane. From this position, the DP lies adjacent to a population of transit-amplifying matrix cells and is thought to emit signals crucial for regulating their proliferation and differentiation into the hair shaft and its channel, the inner root sheath [3,16,25]. The hair shaft is in the center and consists of a medulla, cortex and a cuticle layer. The inner root sheath surrounds the hair shaft and consists of cuticle, Henley and Huxley layers. It is bordered by the outer root sheath layer that contains proliferating cells derived from stem cells in the bulge that feed into the matrix compartment of the bulb. Melanocytes reside above the DP within the epithelial compartment and provide pigmentation to the hair shaft [26]. Morphogenesis initiated during all three waves continues well into postnatal development, when hair shafts eventually erupt from the skin around postnatal day P5 and follicles reach the most advanced stage of postnatal hair growth by days P13–15 [27].

2.3. Regeneration in the hair growth cycle

Once morphogenesis is complete, follicles are prompted to enter the first hair cycle by an unknown stimulus, either presumed to emanate from the DP, or by the absence of continuous growth stimuli from the DP [7]. Fully formed follicles transition into catagen, a destructive phase characterized by profound apoptosis in the epithelial compartment of the lower follicle including the matrix cells and all differentiating layers. The DP remains intact and moves upwards toward the permanent portion of the hair follicle, which contains epithelial and melanocyte stem cells in the bulge [28,29]. Most outer root sheath cells survive as well and move upwards to give rise to a second bulge containing new stem cells and the hair germ of transit-amplifying cells [30]. Whether this movement of DP and outer root sheath is due to active migration or a passive external tug is unknown; regardless, this shift brings the DP into

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close contact with the newly formed bulge and hair germ around P19 in the first hair cycle. After a short period of rest until P21, the DP emits signals that induce stem cell activation and proliferation of hair germ cells that grow down together with the DP to generate a new complete follicle, resembling the activation of epidermal stem cells during embryonic hair follicle induction [27,31].

3. Mesenchymal–epithelial interactions during embryonic hair follicle formation

3.1. Integrative overview of inductive signals and events

The early stages of hair follicle formation involve the tight temporal and spatial regulation of inductive signals in what is thought to be a sequential process of secreted molecules alternating from epidermis and dermis [4]. However, efforts to definitively place the major players such as Wnt, Eda, Fgf, and Bmp in such a cascade are complicated by the multifactorial nature of these interactions and the limited time frame in which these exchanges occur (Fig. 1). Nevertheless, widespread Wnt ligand expression in the epidermis seems to be most upstream event (Fig. 1A) [32]. Secreted Wnts from the epidermis are thought to incite similarly broad Wnt signaling activity within the dermis [32,33], which could in turn drive expression of the elusive first dermal signal(s) necessary to bring about hair follicle induction (Fig. 1B) [4,8,16]. Given that the concept of an inductive dermis was first described many years ago [34,35], it is remarkable that the underlying molecular mechanisms remain obscure. However, a singular epithelial signal promoting dermal cell condensation has not been definitively described either; rather, a number of molecules are thought to promote condensate formation and maintenance (discussed below) [4]. Therefore, it is possible that multiple dermal factors are involved to initiate induction as well.

Multiple molecular markers such as Wnt10b, Edar, Dkk4 and K17 pattern the epidermis before any visible signs of hair placodes [36–39]. Similarly, beneath these epidermal "pre-placodes", new markers such as Sox2 and Sdc1 identify groups of specialized dermal cells [40–42]. At this point in development, parsing out the precise timing and function of each signaling molecule or other genes within the greater scheme of mesenchymal–epithelial interactions becomes difficult because they appear virtually simultaneously. As a result, a comprehensive understanding of how all pathways interact remains incomplete. In the following chapter we provide a detailed discussion of individual signaling pathways implicated in morphogenesis, while noting confirmed upstream and downstream effectors, in an attempt to piece together a model of how these molecules cooperate during hair induction. These relationships are further depicted in Fig. 1C.

The factors that specifically promote follicle growth after induction are slightly more well-defined, since several mutants exist in which hair follicles are induced, but do not mature. In this regard, epithelial Shh and Pdgfa, in addition to Fgf and Tgfb2 ligands emitted from the dermis, are central to promoting hair germ formation (Fig. 1D). A balance of dermal Inhba (activin-βA) secretion and epidermal follistatin expression is similarly important for early progression of hair peg growth (Fig. 1E). In the future, advances in molecular analysis and tools to genetically and/or inducibly target specific compartments at precise time points during hair development will be invaluable to define the subtext underlying epidermal–dermal conversations.

3.2. Inductive signals in embryonic skin

The foundations of modern skin and hair development research were established many years ago by a "cut-and-paste" approach (reviewed in [8,9]). These classic experiments employed tissue recombination techniques to explore the functional basis of mesenchymal–epithelial interactions in skin appendage formation. Epidermal and dermal layers were separated from early mouse embryos, and recombined such that dermis from the hairy back was paired with epidermis from a glabrous region (e.g. hairless foot pad) – or vice versa – before further culture and assessment of hair growth [34,35]. The results of these grafts revealed that only dermis from hairy mouse backskin induced appendage formation, but dermis from hairless regions did not, regardless of the origin of the epidermal tissue. Therefore the inductive potential lies within the dermis, since the origin of dermal tissue dictated whether skin appendages developed.

Morphologically recognizable hair placodes in backskin first appear around E14.5, along with concomitant expression of signaling genes [4,16], and many studies have looked into the roles of these factors in orchestrating follicle induction and subsequent hair formation. The functions of canonical Wnt/β-catenin signaling [43] in epidermis and dermis are especially well-characterized, and it is clear that this pathway is necessary for hair induction [44]. Mutant mice lacking the transcription factor Lef1, a β-catenin binding partner, formed only rudimentary mammary gland, tooth and hair structures providing early evidence of the central role of Wnt signaling in skin appendage development [45]. Subsequent studies confirmed Lef1 activation modulates hair growth: transgenic Lef1 overexpression in epidermis resulted in pelage follicle crowding and ectopic hair growth within other epithelial tissues [46]. Further recombination experiments using wild-type and knockout skin demonstrated a selective requirement for dermal Lef1 expression in mediating normal hair growth [47]. In direct studies of Wnt signaling, transgenic expression of stabilized β-catenin in the epidermis led to de novo hair follicle formation [48], an effect confirmed later with inducible expression of stable β-catenin or epidermal deletion of the intracellular β-catenin inhibitor APC [49–51]. Moreover, early and sustained Wnt activation by epidermal expression of constitutively active β-catenin resulted in increased dermal fibroblast proliferation, precocious placode formation and later switched the entire epidermis to a hair fate or induced excessive, ectopic follicles [52–54]. Correspondingly, selective β-catenin ablation in the epidermis entirely prevented epithelial placode formation [33,55]. Forced expression of constitutively activated β-catenin within the dermis led to major skin phenotypes as well: overproliferation of mesenchymal fibroblasts and excessive follicle morphogenesis following precocious dermal condensate establishment [32]. Thus, a role for Wnt signaling in hair induction is well-established.

Wnt signaling reporter mouse lines have been particularly helpful for defining dynamic patterns of Wnt signaling activity during skin development [33,56–58]. Broad dermal activity driven by widespread epidermal Wnt ligand secretion (Fig. 1A) [32] precedes Wnt signaling in epidermal placodes [33]. Ablation of dermal β-catenin prior to hair induction precludes the expression of any placode markers by the epidermis and results in the failure of first wave hair formation. This suggests that widespread Wnt signaling in dermal cells regulates the first signal(s) to directly or indirectly promote hair fate specification in the epidermis (Fig. 1B) [32,59,60]. Concomitant with Wnt signaling activity in pre-placodes, dermal Wnt activity becomes intensified in underlying dermal condensates. Interestingly, ablating β-catenin in placodes abrogated this focused Wnt activity and resulted in a failure of dermal condensate formation [33,55]. The mechanisms that specifically support dermal condensate formation are not yet clear; Shh and Pdgfa signaling have been proposed in the past, but epidermal Wnt ligands themselves might also play a central role [4,61]. Wnt10a and Wnt10b are upregulated in the placode as morphogenesis begins and might perpetuate focused Wnt signaling activity within both placode and condensate [36]. Both Wnt5a, produced by dermal condensates,

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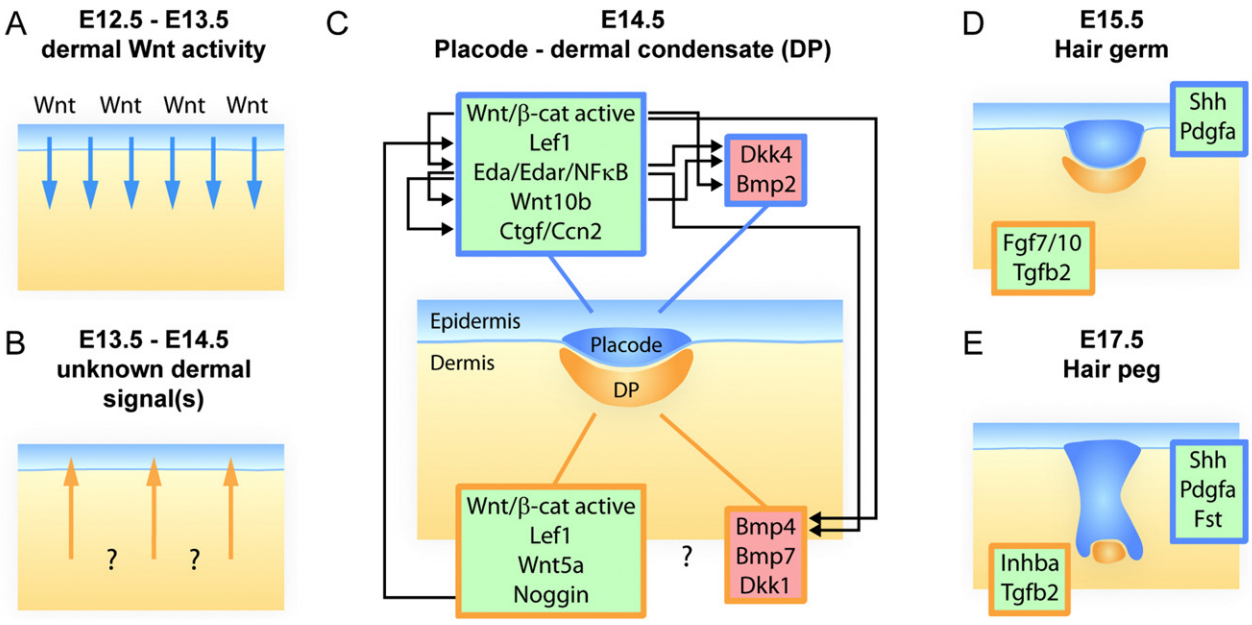

Fig. 1. Mesenchymal–epithelial signal exchange during hair follicle induction. Developmental stages (A–E) are represented schematically. (A) Epidermal Wnts activate dermal Wnt/β-catenin signaling. (B) Unknown dermal signal(s) induce an epidermal response leading to placode formation. (C) Activating (green) and inhibitory (red) signals from placodes and dermal condensates (DP precursors) consolidate pattern formation through reinforcing placode/DP fate and lateral inhibition on neighboring epidermis. The network diagram depicts known hierarchies and regulatory connections between signaling pathways (as described in text). (D and E) Signals regulating hair downgrowth at hair germ and peg stages.

and Wnt10a, turned on in dermis during downgrowth, may contribute as well.

Patterns of Wnt inhibitors in the developing skin are similarly dynamic and compartment specific, in that Dkk1 is expressed in the mesenchyme surrounding follicles during the first stages of downgrowth but is conspicuously absent from the follicle itself [20,36,62]. When this secreted Wnt inhibitor was misexpressed in transgenic epidermis, effectively blocking Wnt signaling in both adjoining epithelial and dermal compartments, the appearance of physical dermal condensates and downgrowths was completely abolished [63]. In contrast, Dkk4 is expressed in the placode of primary wave follicles [38]. It has been proposed to act in a lateral fashion along with BMP ligands to affect placode spacing (to be discussed further below). Intriguingly, overexpression of this factor affects only secondary wave hair morphogenesis while primary guard hairs form normally [64]. The role that these inhibitors play in compartmental crosstalk remains to be clarified.

In addition to Wnt, Ectodysplasin (Eda) signaling is similarly essential for hair follicle induction [6,65]. Eda is a Tnf family ligand [66] that signals through downstream NFκB transcriptional activation after binding to the corresponding Ectodysplasin receptor (Edar) [67,68]. The central role Eda signaling plays in skin appendage morphogenesis was first recognized because mutations in pathway components lead to human disorders of hair, tooth, and mammary bud formation [69]. Mouse models of mutated Edar (*downless*) or ligand Eda (*tabby*) have similar phenotypes [70,71], and are characterized by a sparse coat and absent guard hair formation [65]. During embryonic stages, Eda is widely detectable throughout the epidermis while Edar expression becomes confined to early placode structures. As development continues, Eda expression is progressively confined to the interfollicular epidermis [72]. Because both ligand and receptor are expressed only by the epidermis, Edar signaling appears to act as a purely intraepithelial method of communication, and indeed a number of studies suggest that this pathway is important for placode stabilization and patterning, but not necessarily for initial placode induction [33,73].

Recently the timing and hierarchy of Eda signaling with respect to Wnt/β-catenin signaling was clarified. Using reporter mice for both β-catenin and NFκB activity revealed that Wnt signaling precedes Edar activation, and crossing reporters with knockouts confirmed that Wnt signaling could be activated in the absence of Eda [33]. Conversely, inhibiting Wnt precludes Edar expression and NFκB activation, definitively placing Edar signaling downstream of Wnt pathway components during early hair induction (Fig. 1C). Nevertheless, placodal Wnt10b itself is a direct target of NFκB signaling likely reinforcing placode fate stabilization (Fig. 1C) [33]. Additionally, multiple studies found that the expression of Wnt inhibitor Dkk4 appears downstream of Edar signaling [38,64,74]. In terms of facilitating mesenchymal–epithelial interactions, Eda overexpression in Eda null skin explants identified both dermal Bmp4/7 and epidermal Bmp inhibitors to be downstream targets of Edar signaling [75]. This allows a model in which Dkk4 and Bmp4/7 diffuse laterally to act on surrounding interfollicular epidermis to suppress placode induction. In this reaction-diffusion model, the central placode remains unperturbed, thanks to the expression of Bmp inhibitors Ccn2 and Ctgf also downstream of Edar activation [20,22,63,75–77]. Finally, Shh has been identified as a downstream target of Edar signaling [77] which promotes initial follicle growth following induction.

Apart from Wnt and Eda signaling as promoters of hair induction, BMP signaling activity in embryonic skin has an inhibitory role. During early follicle formation, the BMP receptor Bmpr1a is expressed in the epidermal compartment along with BMP2. BMP4 expression is selectively upregulated in dermal condensates [78]. Noggin, a BMP inhibitor, is also expressed from this compartment; a balance of these contradictory signals is thought to fine-tune the dermal messages sent to an epidermal target at this stage of development (Fig. 1C) [79]. Neutralization of BMPs by noggin overexpression stimulated robust formation of excess placodes [80], while constitutive deletion of noggin impaired the induction phase of follicle generation [79,81]. Secondary follicle induction was specifically inhibited in noggin null embryos, and although primary follicles did form, they arrested at an early downgrowth stage

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lacking Lef1 and Shh expression. Interestingly, impaired epidermal BMP signaling in receptor-null mice promoted accelerated placode development, but was not sufficient to drive excessive follicle formation [82]. To add further complexity, when BMP signaling was abnormally sustained in noggin null skin, it could act back on the epidermal compartment to downregulate Lef1 and Wnt/β-catenin activity [83]. Such observations highlight the complex, overlapping nature of the signals involved in this process, and the intricate balance that needs to be maintained for successful morphogenesis.

Besides Wnt, Eda, and BMP pathways as major mediators of follicle induction, Fgf signaling has been implicated as well, although its role is less clearly defined. Multiple receptor and ligand isoforms are present during the early stages of hair development [84–88]. Transgenic mice expressing a soluble, dominant-negative Fgfr2IIIb isoform failed to develop hair [89], and Fgfr2IIIb knockout mice displayed delayed induction suggesting that Fgf ligands work to promote placode establishment [90,91]. However, more recent investigations conclude that Fgf signaling actually deters induction. Immunostaining for Fgfr2IIIb reveals widespread expression throughout E13.5 epidermis, and then subsequent downregulation in placodes [42]. The role of Fgf signaling in normal hair follicle induction thus requires further study and clarification.

3.3. Initial growth after induction

After induction, placode cells start to proliferate and generate morphologically recognizable downgrowths under the direction of two central signaling pathways: Shh and Pdgf. Shh is first expressed in the developed placode and then localized to the tip of the downgrowing bulb in contact with the DP as development proceeds [78,92]. The Shh receptor Patched is expressed by both epidermal and dermal compartments from an early stage [61]. Shh knockout mice revealed an important role for this signaling pathway in mediating early hair formation [93,94], since hair germs arrested at the early downgrowth stage. Both epidermal and dermal components of these early follicles were already recognizable suggesting that Shh signaling, while dispensable for induction, is crucial for these slightly later stages. To place this pathway in the context of mesenchymal–epithelial interactions, studies used epithelial or dermal-specific ablation of primary cilia components to effectively abrogate Shh signaling separately within each compartment [95,96]. Only dermal-specific knockout mice had a similar hair phenotype as Shh mutants, suggesting that secreted Shh activates effector pathways in a responsive dermis that directly or indirectly supports placode proliferation (Fig. 1D). Very recently, studies in which Smoothened was knocked out in early embryonic dermis have conclusively proven that Shh signaling within dermal condensate cells is crucial for DP development and subsequent hair follicle maturation [97]. Earlier studies of Shh pathway knockouts found normal Wnt10b, Lef1, and Bmp2/4 expression in arrested follicles, indicating that hedgehog signaling either lies downstream or functions independently of these inductive molecules [93,94]. Complementary analyses have confirmed abrogated Shh expression in mice lacking epithelial Wnt or Eda, thus implicating it as a target [55,73–75,77]. However, other dermal factors such as Wnt5a and Pdgf receptor Pdgfra were found to be dysregulated in Shh null follicles [36,61]. Wnt5a expression was completely missing from stalled follicles in Shh mutants, while Pdgfra expressing dermal cells were still present but abnormally dispersed [61]. Since these mice displayed normal Pdgfa ligand expression, the study concluded that downstream targets of Shh signaling within the dermis mediate Pdgf responsiveness and the effects of these two pathways are jointly important for maintenance of the DP.

The role of Pdgf signaling in hair morphogenesis was recognized because Pdgfa knockout mice have sparse coats that degenerate with age. This system provides a clear example of mesenchymal–epithelial interactions, as the ligand is secreted solely by epidermis and the Pdgfra receptor is uniquely expressed in the dermis (Fig. 1D) [61]. Pdgfa expression is initially robust and widespread in E13.5 epidermis before becoming concentrated in early stage placodes [61]. On the dermal side, Pdgfra expression is broadly present throughout the upper dermis early on, but becomes progressively restricted to cells within the DP and along the dermal sheath. A significant percentage of Pdgfa knockout mice die during embryogenesis, but those that survive display abnormally sparse hair and thin skin phenotypes due to diminished white adipose tissue stores. The hair follicles that do appear form normally, suggesting that the signaling pathway is not essential for induction, but the primary coat cannot be maintained and the secondary coat, which usually appears at the first postnatal anagen starting after day P21, is never generated [61]. Pdgfra knockouts die during embryogenesis, but analysis of early skin reveals that follicles form normally, confirming that this signaling axis is not necessarily involved in induction.

Tgfb signaling also promotes hair germ growth; in particular, mesenchymally-expressed Tgfb2 acts on epithelial receptors (Fig. 1D) [98–100]. Full Tgfb2 knockout mice displayed delayed and/or arrested follicle growth at E18.5 reminiscent of Shh null mutants. Furthermore, culturing skin explants in vitro with exogenous Tgfb2 promoted excessive follicle growth [101]. Finally, a role of Tgfb/Activin signaling in hair morphogenesis was recognized because Inhba (activin-βA) ligand knockout mice lack vibrissae at birth [102,103]. Moreover, epidermal-specific receptor knockout mice produced fewer and misshapen follicles that degenerate over time, suggesting dermally-generated ligands are needed to direct both early and late stages of differentiation within the epidermal compartment [104]. The related molecule follistatin, which inhibits activin and Bmp ligands, is expressed from the epithelial compartment and has been investigated in the context of hair growth as well. Surprisingly, full knockouts resemble Inhba knockouts, with fewer, stunted follicles at birth. These findings suggest follistatin works to fine-tune inputs from separate Tgf signaling avenues before morphogenesis can move forward [105,106].

From several of the above-mentioned studies the idea emerges that varying input from multiple signaling cascades leads to the specification of unique hair types. For example, mouse models with compromised Edar signaling lack only guard hairs, indicating that this cascade is uniquely necessary for first wave follicle induction [37]. Conversely, only guard hairs can form in the absence of noggin [81], suggesting that inhibition of Bmp signaling is distinctly required for second and third wave induction. When Shh is overexpressed in the epidermis, both first and second wave follicles are missing, and only third wave zigzag follicles are induced to form [107]. Unique gene expression profiles within the mesenchymal component of the HF specify hair type as well [40]. A differential requirement for Wnt signaling in either compartment has not yet been described, except that epidermal overexpression of Dkk4 appears to affect only second wave morphogenesis [64]. Taken together, evidence from these mutants suggests that the correct balance of morphogens is necessary for the development of discrete hair types, adding yet another layer of complexity for defining a hierarchy of the central signaling pathways implicated in hair formation.

4. Postnatal hair follicle induction capacity

4.1. Inductive capacity of mature DP

Dermal condensates in embryonic hair follicles are precursor cells of the DP in fully formed hair follicles. Although it is believed

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that dermal condensates require stimuli from the placode to form, mature DP cells retain hair inducing activity independent of placodal signals. Early studies demonstrated that microdissected DPs could induce new hair growth after transplantation into glabrous skin of the foot pad [108]. Similarly, adult rat DPs from pelage follicles were microdissected, cultured as single cells and then implanted as cell clumps below foot pad epidermis to induce hair follicle formation from overlying afollicular epidermis [109]. Subsequent refinement of hair induction protocols by growing hairs at the skin surface in chamber grafts [110] or deep in the subcutaneous skin tissue [111] now allows hair induction to be assessed for hundreds of hairs simultaneously. Using such methods, pure DP cells isolated based on fluorescent markers from postnatal backskin retained hair induction capacity when transplanted together with postnatal epidermal cells [14,40].

Interestingly, the hair type origin of DP cells also determines the type of experimentally induced hair follicles; for example, whisker DP cells induce whisker-like follicles on mouse ears [109]. Recent transcriptional profiling of DP cells from pelage follicles generated a DP gene signature [14] and DPs from pelage hair cell types retain a core signature but also exhibit distinct gene expression profiles [40]. Sox2, for example, is robustly expressed in guard and awl/auchene DP, but not in zigzag DP. The functional importance of this difference was recently illustrated by isolating pelage DP based on Sox2 expression prior to using these cells in separate hair-reconstitution assays. Isolated Sox2-negative DPs, when combined with keratinocytes in chamber graft assays, produced only zigzag type hairs. These experiments highlight the importance of mesenchymal–epithelial interactions in hair formation and provide powerful evidence that such interactions help drive hair type specification during morphogenesis [40].

4.2. Adult follicle neogenesis after wounding

According to common knowledge, de novo hair follicle morphogenesis is a one-time affair that is limited to embryogenesis and early postnatal development. However, over half a century ago observations in adult rabbits, mice and even humans suggested the potential of new hair follicle formation in the context of a wound response [112–115]. Recently wounding-induced hair follicle formation was confirmed with elegant experiments in mice, in which definitive genetic fate mapping demonstrated the origin of new follicles, including their stem cells, from neighboring epidermal cells during reepithelialization [116]. Ablation of Wnt signaling in the healing wound completely abrogated new hair formation. The potential role of an inductive mesenchyme and the origin of the newly formed DPs has yet to be examined in this context.

5. Compartmental crosstalk during postnatal hair growth

After the early stages of downgrowth are complete, the DP is thought to direct neighboring epithelial matrix cells to proliferate and differentiate into the multiple cell types that form the hair shaft and its channel [3]. Several signaling programs central to induction are involved in these later stages of follicle maturation as well (Fig. 2); for example, Wnt signaling activity and nuclear Lef1 and β-catenin expression in maturing hair shaft precursors point to an important role of this pathway [56,117]. Hair shaft keratins are regulated by Wnt signaling activity [117], and forced activation of Wnt signaling drove matrix cells into differentiating hair masses resembling human benign hair tumors [48,118]. Inducible β-catenin ablation to block Wnt signaling activity in the matrix cells specifically during the hair growth phase has not yet been performed. However, active signaling in the dermal compartment is important at this stage; cultured DP cells grown in the presence

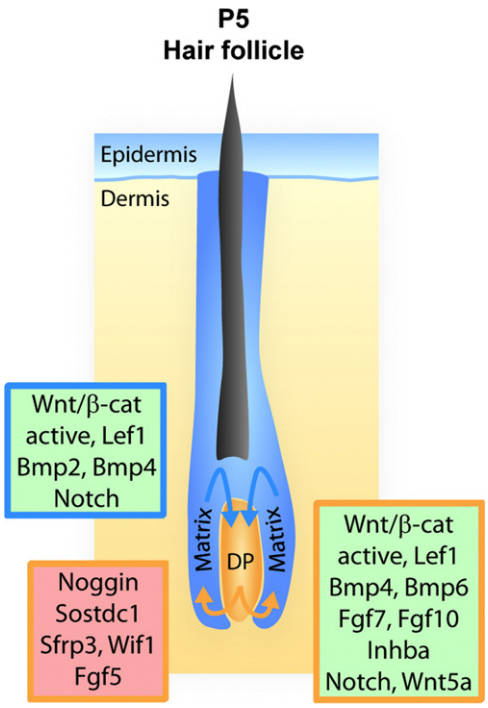

Fig. 2. Signaling between matrix and DP during hair follicle growth. Multiple positive and negative regulators are in both compartments that may also signal in an autocrine fashion.

of Wnt ligands retained hair inductive capabilities [119], and postnatal ablation of β-catenin in the DP compromised hair growth [120].

The importance of Bmp signaling is also reiterated during postnatal hair growth. Follicles formed when the Bmp receptor was selectively deleted within the epithelial compartment, but matrix cells were unable to undergo the proper program of maturation and differentiation [82,121,122]. Ultimately, highly abnormal follicles were generated because of an inherent inability of epithelial progenitors to stabilize Lef1 and activate Wnt signaling. In other investigations of Bmp signaling in postnatal growth, ligand overexpression inhibited proliferation within the outer root sheath resulting in small and misshapen follicles that were unable to regenerate [123]. Overexpression of the Bmp inhibitor noggin leads to excessive matrix cell proliferation and prevented hair shaft maturation [124]. An important role for Bmp activity within DP cells exists as well [125]. Ablation of Bmp signaling in isolated DP cells abolished their ability to organize hair growth in a chamber graft assay, suggesting that Bmp activity within the DP is required for instructive capabilities.

Another pathway important for organizing hair growth during postnatal morphogenesis is Fgf signaling through Fgf7/Fgf10 ligands [86]. Neonatal Fgfr2IIIb null skin, insensitive to both ligands, displayed cystic or misaligned follicle growth when cultured in grafting experiments [91]. Finally, Notch signaling also appears to participate in hair maturation, since mice with disrupted dermal Notch signaling developed intrinsic hair shaft defects [126]. Decreased Wnt5a in DP and reduced Foxn1 in matrix cells were part of the mechanism behind this phenotype. Notch signaling within matrix progenitors is also necessary to maintain proper terminal hair differentiation [127,128].

Several intrinsic transcriptional regulators such as Cutl1, Gata3, Hoxc13, Foxn1 and Msx2 directly affect hair shaft differentiation, structure and shape (reviewed in [2]). Whether mesenchymal–epithelial interactions are involved or these factors function in a compartment-autonomous manner remains to be

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determined. Egf, Igf and Tgfa signaling pathway activation can also affect hair shape [2].

After the anagen growth period, follicles enter the catagen destruction phase, which also seems to be regulated by mesenchymal–epithelial interactions and influences from the macroenvironment [16]. Knockout mice lacking Fgf5, which is expressed in DP, are characterized by abnormally long hair due to a prolonged anagen phase, indicating that signaling through this ligand promotes catagen entry [129]. Other examples of factors that advance the anagen/catagen transition include Bdnf, IL1b, Ntf3, Tgfb1 and Tnf, while Hgf, Igf1 and Vegf promote anagen maintenance (reviewed in [130,131]). The direct source of origin and the potential involvement of mesenchymal–epithelial interactions for many of these molecules remain to be clarified.

6. Signals during hair regeneration

6.1. Signals from the dermal papilla

During the anagen growth phase DP cells in the bulb are far removed from bulge epithelial stem cells in the upper part of the follicle, and most likely do not contribute to regulation of stem cell quiescence [15,132,133]. Other cell types in the immediate stem cell microenvironment or niche, such as endothelial cells, Schwann cells and nerve endings, and dermal sheath cells are considered to provide signals keeping the stem cells in a quiescent state [31,134]. Although tantalizing gene expression analyses in the stem cells suggest such a model [12,13,15], direct evidence is lacking. The same analyses proposed secreted factors generated by stem cells may regulate their own behavior in an autocrine fashion. In addition, bulge epithelial stem cells affect neighboring melanocyte stem cells [135,136] and muscle progenitor cells just outside the bulge that give rise to the arrector pili muscle [137], and in return these cells may influence epithelial stem cell behavior as well. On the other hand, many stem cell intrinsic factors, such as transcription factors Lhx2, Nfatc1, Runx1, Sox9, Stat3, Tcf3/Tcf4 were shown in loss of function studies to directly affect stem cell quiescence and activation, and subsequent hair regrowth during the hair cycle [23,138–144]. Again, direct regulation of these factors by interactions of the epithelial stem cells with the neighboring mesenchyme has not been established yet, leaving the possibility that these essential genes are regulated cell-autonomously and not necessarily influenced by mesenchymal–epithelial interactions.

As the hair cycle ensues, DP cells move upwards toward the skin surface during the catagen destruction phase and come to rest next to the bulge stem cells and hair germ progenitor cells during the telogen resting phase. It is not clear whether DP cells join the niche efforts to regulate stem cell quiescence, but historically the presence of DP cells next to the stem cell compartment is considered essential for activating stem/germ cells to regenerate the follicle in a new anagen growth (Fig. 3) [3]. While conceptually appealing, this model lacked substantiating evidence until very recently because of the absence of DP-specific inducible gene targeting tools to directly interrogate the role of genes in the DP for stem cell activation in the bulge. Nevertheless, without such tools, the activating role of the DP was confirmed by using laser ablation to selectively target DP cells in vivo during hair cycling [145]. After DP cells were physically disrupted corresponding follicles became quiescent while neighboring unaffected follicles continued to cycle. Other examples supporting the instructive role of DP cells during hair re-growth came from hairless (Hr) and vitamin D receptor (Vdr) mutant mice, in which DP cells fail to move upwards toward the bulge during the catagen destruction phase, leaving DP cells stranded deep in the dermis [146,147]. New hair follicle regeneration at the end of telogen is absent, suggesting that the presence of DP cells next to bulge stem cells is important for inducing new hair re-growth. More

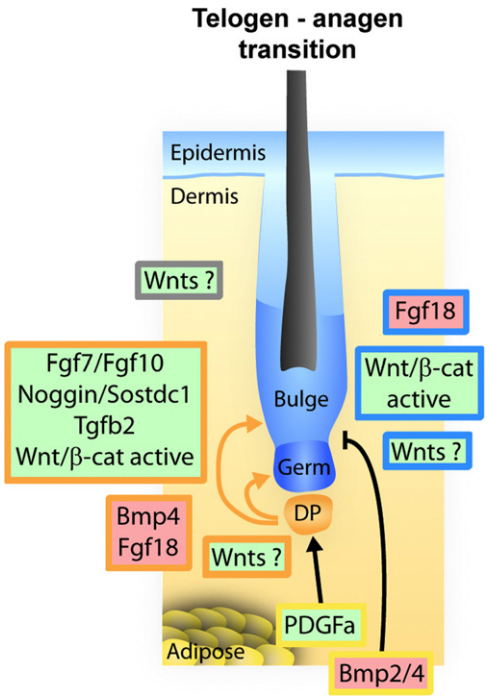

Fig. 3. Signals regulating stem cell quiescence and activation during the hair cycle. Bmp2/4 from DP/adipose tissue and Fgf18 from bulge/DP inhibit stem cell activation. Activation of Wnt signaling in the bulge and secreted Fgf7/10 and Bmp inhibitors from the DP activate stem cells to re-grow a new follicle during hair regeneration.

recent, albeit indirect evidence comes from work demonstrating that DP-derived Fgf7 and Fgf10 are involved in promoting hair follicle regeneration during the anagen to telogen transition [148]. Exogenously supplied Fgf7, normally expressed in DP cells [14], induced bulge/hair germ proliferation, suggesting that DP-derived Fgf7 could be a stem cell activating signal (Fig. 3). Another cytokine that could act on the stem cells both in an autocrine fashion and through mesenchymal–epithelial interactions is Fgf18, which was found to be expressed in bulge cells and to inhibit bulge cell proliferation in vitro [13]. More recently, Fgf18 expression was described as high in both DP and bulge cells during mid-telogen, and ablation of the factor in the stem cell compartment prompted rapid progression into active hair growth (Fig. 3). Additionally, Fgf18 could suppress hair growth in studies involving the injection of recombinant Fgf18 protein [149]. Genetic tools to selectively target genes of interest in the DP will be necessary to understand the molecular mechanisms behind DP-induced stem cell activation during hair cycling.

Many recent studies have also demonstrated a critical role for Wnt and Bmp signaling during hair regeneration in terms of controlling stem cell quiescence and activation [28,150,151]. Forced activation of Wnt signaling through expression of stabilized β-catenin led to precocious stem cell activation in the bulge [50,152,153]. Conditional and inducible ablation of β-catenin in the bulge during telogen showed a loss of quiescence and depletion of stem cells [152]. Therefore inhibition of Wnt signaling by Tcf3 within the stem cells [142] and by secreted Wnt inhibitors from the stem cells [15] and the niche [148] appear to be crucial for maintaining stem cell quiescence, while activation of Wnt signaling is required for the transition to a new hair growth phase (Fig. 3). In a reversed role to Wnt signaling, active Bmp signaling is required for stem cell quiescence, since ablation of Bmp receptors in stem cells leads to aberrant stem cell activation [154,155]. It appears that for stem cell activation and new hair follicle regrowth to occur, upregulation of Bmp inhibitors in the DP [148,156] and downregulation

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of long-range Bmp signals from deep in the dermis (see below) have to coincide with activation of Wnt signaling in the bulge (Fig. 3).

Most recent evidence also implicated an essential role of Tgfb signaling in the stem cell compartment. By selectively ablating the Tgfbr2 receptor expressed in stem cells, these studies demonstrated that Tgfb2 ligands generated in the DP act on the epithelial compartment to promote a switch from quiescence to active regeneration [157]. Downstream of activated Tgfb2 signaling, target genes suppress propagation of Bmp signaling and allow onset of a new round of follicle cycling. This is consistent with earlier studies, in which authors were able to provoke premature anagen by injecting recombinant Tgfb into skin [101].

6.2. Role of the macroenvironment

Besides influences from the local stem cell microenvironment, fat tissue deeper in the dermis was recently described as a heretofore unrecognized niche cell population, capable of secreting factors to influence hair cycling from a distance. Fat-derived Pdgf in particular was proposed to act on DP cells which in turn regulate induction of follicle regeneration in the hair cycle (Fig. 3) [158]. Mutant mice with defects in skin adipocyte precursor cells, which normally express high levels of Pdgfa ligand, lacked Pdgfra receptor activation in DP cells. Hair re-growth failed during the cycle, but could be recovered by injecting beads soaked in Pdgfa, suggesting that fat-stimulated activation of this signaling pathway in the DP niche elicits downstream events to trigger follicle regeneration.

Influences from fat may regulate the behavior of cohorts of hair follicles at once, providing macroenvironmental cues that can affect larger domains of the hair coat in which all follicles cycle together in a dynamic fashion. Such a model is supported by recent findings of cyclical Bmp expression in the fat domain [159]. High Bmp levels reach the bulge area and help to keep Wnt-repressed stem cells quiescent, thereby promoting a refractory telogen phase. Together with activation of Wnt/β-catenin signaling, widespread downregulation of long-range Bmp signals then promotes stem cell activation and new hair re-growth during an "induction competent" phase [160].

7. Concluding remarks

Hair follicle morphogenesis is an excellent model system in which to explore universal developmental themes, and studies of mesenchymal–epithelial interactions in this context have been particularly robust. As described in this review, numerous aspects of the communication between epidermis and dermis during hair induction, growth and regeneration have been uncovered. Nevertheless, despite decades of increasingly meticulous investigation, many details of the complex mechanisms driving hair follicle morphogenesis and cycling remain obscure. Studies have been hindered by multiple signaling isoforms that impart redundancy, as well as intricate pathway intersections and feedback loops that are difficult to untangle using mouse models. Two central mysteries that remain to be explored are the nature of the first dermal signal(s) during embryonic hair follicle induction and the activating signal(s) from DP cells during hair regeneration in the cycle. Clarification of timing, origins, and targets of important signaling pathway components will be necessary as well. Additionally, advances have been hampered by the absence of tools to specifically manipulate gene expression in inductive DP precursors during early formation stages and adult DP cells during regeneration. Compartment–specific genetic drivers to target the placode and lineages in the mature hair follicle will be useful as well. As our tools continue to be refined, so too will our understanding of how epithelial and mesenchymal tissues cooperate to create such elaborate and patterned structures as the hair follicle, imparting a greater understanding of developmental paradigms and potentially information about hair growth that will be useful in clinical applications.

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