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Hereditary hair loss and the ancient signaling pathways that regulate ectodermal appendage formation

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All epidermal appendages, including hair, teeth, and nails, begin as a thickening of the ectoderm, called a placode. The placode arises from a primary induction signal that is sent from the underlying mesenchyme to the overlying epidermis. In mammals, the precise arrangement of hair follicles in the skin is due to the amount and distribution of signals that promote and inhibit hair placode formation. Continued development of a hair follicle after placode formation requires a complex cross-talk between the mesenchyme and epidermis. Here, I will review recent studies in humans and mice that have increased our understanding of the role of these signaling pathways in normal development and in hereditary hair loss syndromes. The study of normal hair development may suggest ways to restore or eliminate hair and might identify possible targets for the therapy of basal cell carcinoma, a cancer which strongly resembles embryonic hair follicles.

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Placode induction

The skin is an essential barrier protecting the body from environmental assaults such as UV radiation, water loss and microbial infection. In mammals, hair plays other important roles as well, including camouflage, tactile sensation, sebum dispersion, social communication and the regulation of body temperature. Hair follicle formation begins at the 10th week of human gestation and continues into the perinatal period. Hair follicle morphogenesis can be divided into several phases, the first of which is the formation of the placode, a thickening of the epidermis. All epidermal appendages, including hair, teeth, and nails, begin as a placode.

Through classical tissue recombination experiments, it has been shown that placode formation in the ectoderm is triggered by a signal from cells in the underlying mesenchyme (1). In response to the signal, the epidermal cells undergo changes in shape and become more densely packed, thickening the ectoderm locally where a hair follicle will form (2). This characteristic morphology is classified as stage 1 of hair follicle morphogenesis.

In the dorsum, the mesenchymal cells producing the placode inductive signal originate in the dermomyotome of the somites, which are blocks of mesoderm that flank the embryonic spinal cord (3). These mesoderm cells proliferate, populate the skin and signal to the ectoderm. Although the composition of the primary inductive signal for placode formation is still not certain, the Wnt signaling pathway plays a major role at this stage.

Wnts belong to the wingless family of extracellular signaling proteins (4). In the canonical Wnt signaling pathway, Wnt binds to its receptor,

frizzled, on the cell surface, which leads to the stabilization of intracellular β-catenin (5). Deletion of *β-catenin* in the mouse epidermis results in the failure to produce hair follicle placodes (6). Conversely, the expression of constitutively stabilized β-catenin in the mouse epidermis early during development causes the entire epidermis to adopt a hair follicle fate, as shown by precocious and widespread expression of placode markers and, later, the uniform expression of hair shaft specific keratins (7, 8). Despite this, hair follicle morphogenesis arrests in these mice at a placode-like stage, showing that this pathway cannot remain constitutively active if the next stage of development is to proceed normally (7, 8).

Studies in mice have now conclusively shown that hair follicles can form *de novo* in adults after wounding, a possibility that has been long suspected in several mammals, including humans (9, 10). The cells forming the *de novo* hair follicles come from the re-epithelialized interfollicular epidermis, not from stem cells in pre-existing hair follicles (9). Blocking Wnt signaling completely prevented new follicle formation after wounding in the mouse model, while overexpressing Wnt increased the number of new hair follicles (9). This study suggests that embryonic pathways for hair follicle morphogenesis can be reactivated in the adult skin. In the future, it might be possible to harness these pathways to regenerate hair.

Placode positioning and orientation

The regular spacing of placodes is determined by a reaction–diffusion mechanism that involves an activator and an inhibitor linked by a feedback loop, a model initially proposed by Turing in 1952 (11, 12). A recent study in mice has suggested that Wnt and its inhibitor, Dkk, may act as an activator–inhibitor pair in hair follicle formation (13). Wnt signaling induces *Dkk* expression placodes via binding sites for the Wnt-activated transcription factors, TCF and LEF, in the Dkk promoter (13–15). Dkk protein diffuses outward, inhibiting placodal fate in nearby cells, which might have secondarily become placodes (13). In support of this model, a direct relationship is observed between the level of transgenic *Dkk* expression in placodes and the distance between placodes (13).

A non-canonical Wnt pathway may help to orient hair follicles so that they all grow pointing in the same direction, a phenomenon called planar cell polarity (5). This process is best studied in *Drosophila*, where a number of genes have been identified that regulate the polarity of hairs, bristles and photoreceptors. These include *Frizzled*, *Strabismus* and *Flamingo* (16). In mice, homologs of these genes (*Fzd6*, *Vangl2* and *Celsr1*) are expressed asymmetrically, localized to only one side of each cell in the epidermal basal layer, just prior to the placode stage (17). The Wnt receptor, Fzd6, forms a multiprotein complex with Vangl at the cell membrane (17). Their downstream effector is RhoA, not β-catenin (5, 18, 19). Celsr1, an atypical cadherin, is required for the asymmetrical recruitment of Fzd6 and Vangl2 to the membrane (17). Celsr1 promotes cellular adhesion through calcium-dependent, homotypic binding (17, 20). Mutations in these genes in mice cause whorled hair patterns and random orientation of the hair follicles (17, 21).

Maintenance of the placode

A second critical pathway for placode development is the ectodysplasin (Eda) signaling pathway. Eda is a tumor necrosis factor-like signaling molecule that binds to the Eda receptor (EdaR) which is specifically expressed in placodes and activates NF-κB (22–24). In the absence of *Eda*, *EdaR* or *NF-κB*, mouse hair follicles arrest at the earliest stages of placode formation (23). Keratinocytes do show some signs of accumulation and elongation, but clear placodes do not form (23). There is also evidence of increased cell death in these disorganized pre-placodes (23).

Two lines of evidence indicate that Eda signaling is downstream of the primary inductive signal. First, recombinant Eda-A1 protein increases the size of placodes in cultured embryonic mouse skin, but does not cause precocious placode formation (25). Second, *Eda* expression upregulates sonic hedgehog (Shh), a placode marker, but not in the absence of *β-catenin* (6, 26). Thus the role of Eda appears to be to help maintain the placode (23, 25). It may be necessary to have a separate maintenance program, as the reaction–diffusion model predicts that the primary activator will induce its own inhibitor (13). Interestingly, although no placodes formed in the *β-catenin* null embryos, *EdaR* expression was maintained in a placodal pattern in the skin (6). This suggests that *EdaR* expression is responsive to some primary inductive signal, independent of canonical Wnt signaling.

The role of the Eda signaling pathway in hair follicle morphogenesis was first discovered in 1996

through the identification of *Eda* and *EdaR* mutations in human families with hypohidrotic ectodermal dysplasia (HED) (MIM 129490, 224900, 305100) (27, 28). In fact, the discovery of *Eda* mutations in HED was the first molecular analysis of any of the more than 150 clinically distinct ectodermal dysplasia syndromes in humans (27). HED is characterized by sparse hair, missing or abnormal teeth and an inability to sweat due to a lack of sweat glands (27). Recently, through mutagenesis screening, loss-of-function mutations in the zebrafish homologs of *Eda* and *EdaR* were discovered that affect fish scale development (29). Similar to the mouse mutants, early scale placodes can be detected, but they are disorganized, show increased apoptosis and fail to develop further. Thus the role of the Eda signaling pathway in the development of the placode has been remarkably well conserved (30).

Mice with a skin specific knockout mutation of *Lgr4*, a G-protein coupled receptor, have a very similar phenotype as the Eda pathway mutants, suggesting that a G-protein signaling pathway may be required in conjunction with Eda signaling at the early placode stage (31). The primary events required for hair follicle placode formation are summarized in Fig. 1.

Forming the hair germ

The next step in hair follicle morphogenesis is the increased proliferation and subsequent downward growth of the placode cells into the underlying mesenchyme, forming a hair germ which is referred to as stage 2 of hair follicle morphogeneis (1, 3, 32). At the same time, the mesenchyme organizes into a dermal condensate, which will become a structure called the dermal papilla (3, 33). The Shh pathway plays an important role at this stage. *Shh* is a secreted signaling molecule that is expressed specifically in the placode and is upregulated by Wnt and Eda signaling (6, 23, 26, 34). Shh is received by the patched receptor, which is expressed by both the epidermis and the underlying mesenchyme (3, 8, 35, 36). In *Shh* null mice, downgrowth of the placode into the dermis is arrested at stage 2 and the dermal condensate fails to develop (37, 38). Binding of Shh to Patched liberates the activity of Smoothened, which leads to the release and nuclear translocation of Gli2 (39).

Identical defects are observed in mice lacking *Gli2*, a zinc finger transcription factor activated by Shh (38, 40). Transgenic restoration of *Gli2* in just the epidermis is sufficient to restore normal hair follicle development in *Gli2* null mice (38). Gli2 probably promotes keratinocyte downgrowth by activating D type cyclins, which are required for cell cycle progression in G1 of the cell cycle (38, 41, 42). Transgenic restoration of *Gli2* in just the epidermis of Shh null mice increased keratinocyte downgrowth, but did not rescue hair follicle development (38). This shows that Shh signaling activates other targets in the epidermis or mesenchyme, or both, in addition to Gli2.

Gli2 null mice fail to make dermal condensates, but this is rescued when *Gli2* is restored to the epidermis (38). This indicates that signals from the epidermis are required for the formation of the dermal condensate (1, 33). The dermal mesenchyme is also required for the continued development of the hair germ (1, 43). Thus there is a mutually supportive, complex cross-talk required at this phase of hair follicle morphogenesis. On the dermis side at least, this cross-talk is facilitated by a structure called the primary cilium.

Primary cilia are 1–2 μm long microtubule based organelles that form protrusions of the cell membrane into the extracellular space (44). Signaling components, such as the Patched receptor, localize to the primary cilium (45, 46). The primary cilium increases the ability of cells to detect morphogens by expanding the area of surface membrane contacting the extracellular space, as well as by concentrating various signaling components together (47). Ift88 is a protein required for the formation of the intraflagellar transport particle, which is needed to construct the primary cilium (44, 48). Knocking out the Ift88 gene specifically in the dermis of mice prevents primary cilia from forming on mesenchymal cells (43). Hair follicle development in these mice arrests at stage 2, presumably because the mesenchyme is unable to receive critical signals from the epidermis (43). These signals might include platelet derived growth factor, which is expressed by epidermal cells, or Shh itself (33). Defects in primary cilia also underlie the stage 2 arrest of hair follicles observed in laminin-511 knockout mice (49). The major signaling pathways playing a role at the beginning of stage 2 are summarized in Fig. 2.

Hair follicle maturation

The leading edge of the downgrowing keratinocytes that are in contact with the dermal papilla are highly proliferative (3). As the epidermal portion increases in length, the developing hair follicle progresses through stages 3–5 of morphogenesis. In stages 6–8, the hair follicle keratinocytes differentiate into specialized cells. Arranged like the

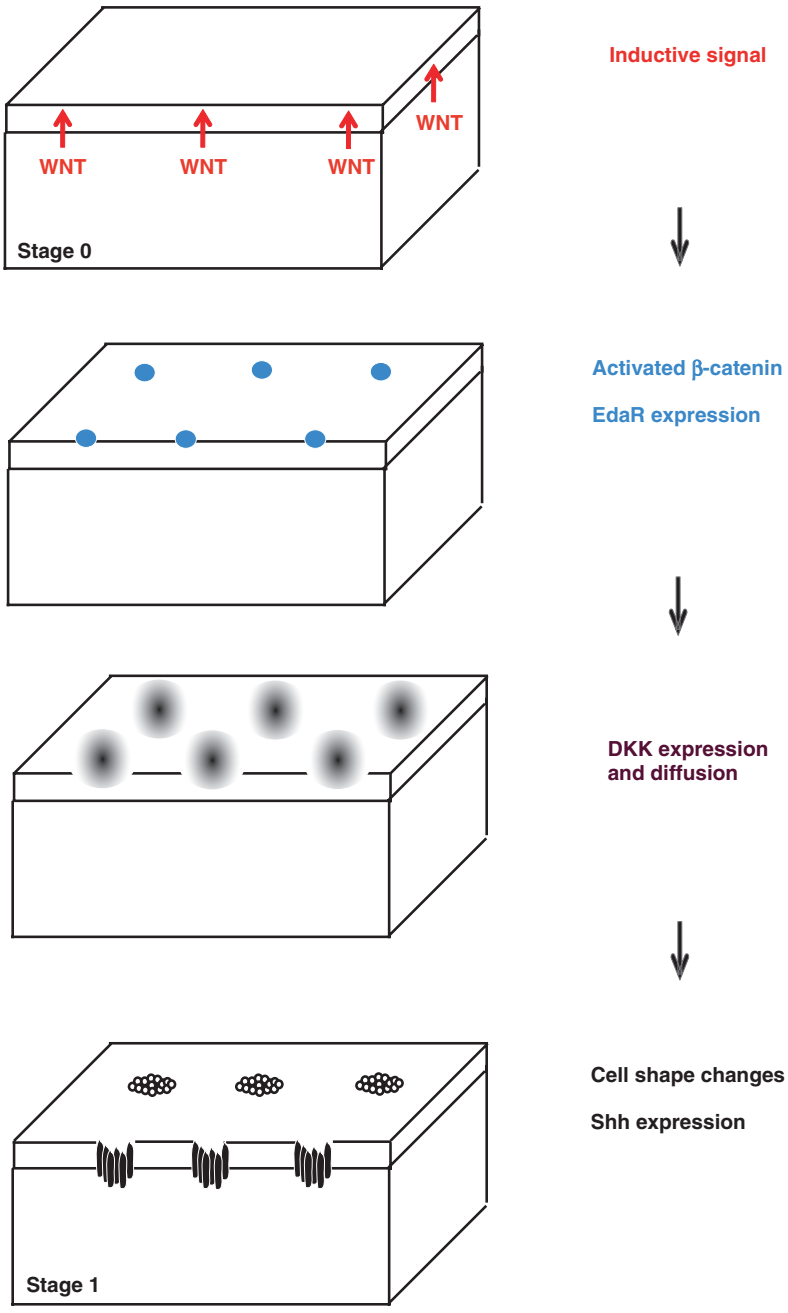

Fig. 1. Summary of key events in the placode induction phase (Stage 0–1). The first step in placode formation is the transmission of an inductive signal from the dermal mesenchyme to the overlying epidermis. Although the composition of the primary inductive signal is still undefined, the signaling molecule, Wnt, plays a critical role. Wnt signaling induces the stabilization of β-catenin, which upregulates gene expression in the cells now fated to become placode cells. One of the genes upregulated is Dkk, which is actually an inhibitor of Wnt signaling Dkk diffuses outward, preventing nearby cells from secondarily adopting a placodal fate. Through an unknown mechanism, the expression of the ectodysplasin receptor (EdaR) is restricted to the pre-placode. Ectodysplasin (Eda) signaling maintains and enhances placode growth. The cells forming the placode elongate and form an indentation into the dermis. The actions of Eda and Wnt trigger expression of the signaling molecule, sonic hedgehog (Shh), in the placode.

skin of an onion, there are eight different layers in the mature hair follicle. From the outside in, the layers include the outer root sheath, the companion layer, three layers of inner root sheath, the hair shaft cuticle, the hair cortex and lastly, the hair medulla at the center (3). The genes mutated in several hereditary hair dysplasias have recently identified new signaling pathways that are required for the correct differentiation of the hair follicle (Table 1).

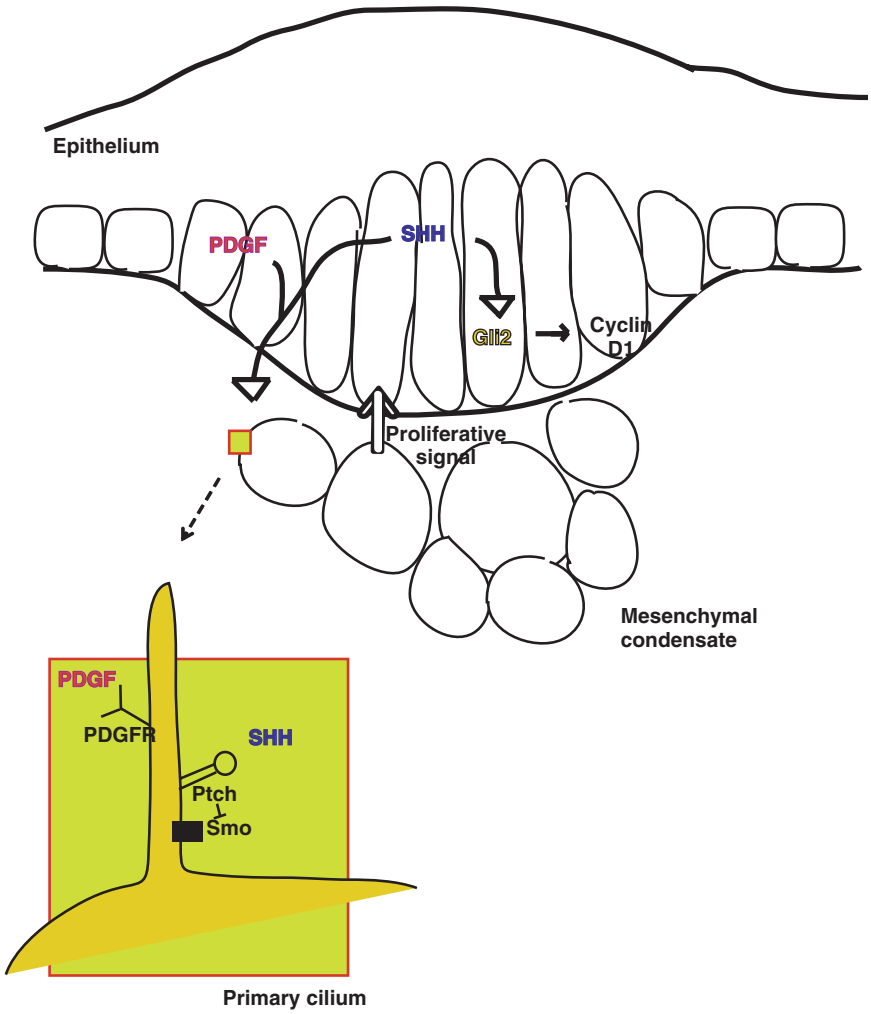

Fig. 2. Cross-talk between the mesenchyme and epidermis in stage 2 hair follicles. Sonic hedgehog (Shh) expression is upregulated in the placode at the end of stage 1. Patched receptors for Shh are expressed in both the placode and the mesenchymal condensate. Patched receptors in the mesenchyme are localized to a structure called the primary cilium. Shh binding to Patched releases Smoothened inhibition, allowing downstream effectors to be activated. In the epidermis, Shh signaling activates Gli2, which upregulates D type cyclins, stimulating keratinocyte proliferation. Proliferation is greatest at the leading edge of the hair germ, where the epidermis directly contacts the mesenchyme. The mesenchyme is required for complete downgrowth. Basal cell carcinomas strongly resemble early stage hair follicles. Loss-of-function mutations in *Patched* and gain-of-function mutations in *Smoothened* are frequently found in this cancer.

Bamforth–Lazarus syndrome (MIM 241850) is a rare, autosomal-recessive condition characterized by cleft palate, congenital hypothyroidism, choanal atresia, bifid epiglottis and spiky hair (50). The hair is sparse with reduced hair shaft diameter and loss of scale patterning (50, 51). Mutations in *TTF-2*, a forkhead/winged-helix domain transcription factor, are responsible for Bamforth–Lazarus syndrome (52, 53). A knockout mutation of the mouse homolog, *Foxe1*, causes disoriented, misaligned and aberrantly shaped hair follicles, beginning after birth (51). Mouse *Foxe1* expression is dependent upon Gli2 and the Shh signaling pathway (51). *Foxe1* may be a direct target, as the *Foxe1* promoter is responsive to Gli2 protein (51).

Tricho-dento-osseous syndrome (MIM 190320) is an autosomal dominant disorder characterized by elongation of the dental pulp chambers, enamel hypoplasia, cranial thickening with obliteration of the frontal and mastoid sinuses, and kinky, curly hair (54). Mutations in *DLX3*, a homeobox transcription factor, are associated with tricho-dento-osseous syndrome (54, 55). Conditional deletion of *Dlx3* specifically in the mouse epidermis caused complete alopecia, due to the failure of the hair shaft and the inner root sheath to form (56). In particular, the inner root sheath specific transcription factor, *Gata3*, and the hair shaft

Table 1. Signaling pathways affected in human hereditary hair dysplasias

Disorder	Hair defects	Gene(s) mutated	Hypothesized signaling pathway
Hypohidrotic ectodermal dysplasia	Sparse hair	Ectodysplasin (Eda), Eda receptor (EdaR), EdaR associated death domain (EdaRDD)	**Eda** – **EdaR** – **EdaRADD** – NF-κB – Shh – Patched – Gli2 – Cyclin D1
Bamforth–Lazarus syndrome	Sparse spiky hair, reduced hair shaft diameter, loss of scale patterning	TTF-2 (Foxe1)	Shh – Patched – Gli2 – **Foxe1**
Tricho-dento-osseous syndrome	Kinky, curly hair	Dlx3	Wnt – Frizzled – β-catenin – Lef1 – **Dlx3** – Gata3 and Hoxc13
Hypotrichosis simplex	Diffuse and progressive hair loss	P2RY5	Lipase H – Lysophosphatidic acid – **P2RY5**
Woolly hair syndrome	Coarse, lusterless, dry and tightly curled hair that lacks root sheath	P2RY5	Lipase H – Lysophosphatidic acid – **P2RY5**

specific homeobox transcription factor, *Hoxc13*, were not expressed in the mutants (56). Chromatin immunoprecipitation assays showed that Lef1 binds the *Dlx3* promoter, indicating that *Dlx3* is a direct target of Wnt signaling (56).

Two groups recently found mutations in the G-protein coupled receptor, *P2RY5*, in two different hereditary hair dysplasias: hypotrichosis simplex (MIM no. 146520) and woolly hair syndrome (MIM 278150, 194300) (57, 58). Hypotrichosis simplex is autosomal recessive, with diffuse and progressive hair loss beginning early in childhood (59, 60). Woolly hair syndrome, without any associated systemic manifestations, can be inherited as either autosomal dominant or recessive (61). It is characterized by coarse, lusterless, dry and tightly curled hair that lacks root sheath components in the bulb (61). *P2RY5* is expressed ubiquitously in the skin, including strongly in the inner root sheath, which anchors and shapes the growing hair shaft (58). Similar sized truncations of the P2RY5 protein were found in both hypotrichosis simplex and woolly hair syndrome families, showing that there is a wide range of expressivity associated with P2RY5 loss-of-function (57, 58).

Several lines of evidence suggest that P2RY5 is a component of a lysophosphatidic signaling pathway that regulates hair growth and shape. The ligand for P2RY5 is lysophosphatidic acid. Topical phosphatidic acid stimulates hair growth in mice (62). Lysophosphatidic acids are produced by lipase H (57, 63). Mutations in lipase H cause another form of hypotrichosis simplex (MIM 604379) (64, 65). As G-protein coupled receptors are frequently used as drug targets, P2RY5 may lend itself to therapies aimed at reducing or stimulating hair growth (58, 66).

Basal cell carcinoma

Because the skin is exposed to high levels of environmental insults, it is the most common site for developing tumors. The most common cancer in individuals of European descent is basal cell carcinoma (BCC) (67). Interestingly, BCCs resemble embryonic hair follicles in morphology and gene expression. Both consist of a *de novo* protrusion of epidermal cells into the dermis (68, 69). Both express outer and inner root sheath markers (70). However, BCCs have no mesenchymal component (70).

The first molecular link between hair follicle development and BCC was found by mapping the gene responsible for nevoid BCC syndrome (71–73). This dominant disorder is characterized by multiple BCCs and maps to the Shh receptor, *Patched* (71–74). Loss-of-heterozygosity of *Patched1* in familial and sporadic BCCs showed that *Patched1* acts as a tumor suppressor. Normally, binding of Shh to Patched releases Smoothened from inhibition, so in the absence of Patched, Smoothened is constitutively active. Gain-of-function mutations in *Smoothened* have also been found in BCC (67). Nearly all BCCs show upregulated Shh signaling (70). BCC has been one of the best illustrations of the connection between developmental pathways and pathways driving tumorigenesis.

Furthering these observations, there is now evidence that the Wnt signaling pathway also plays a role in BCC (70). BCCs have increased levels of stabilized β-catenin and in a mouse model, the Wnt inhibitor, *Dkk1* inhibited tumor formation (70). Because BCC is driven by mutations in hedgehog pathway components, hedgehog signaling must upregulate the Wnt signaling pathway in this cancer, a reversal of normal embryonic development. Dissecting the complex genetic networks that are activated in BCC and determining how these differ from normal development may reveal basic principles of tumorigenesis, applicable to a wide variety of cancers.

Conclusions

Hirsutism, graying, alopecia and other disorders of human hair follicles play a significant role in the human social experience. In the future, the challenge of clinicians will be to harness what we learn about the developmental biology of hair follicles to safely treat these disorders. Hair follicles are a rich source of stem cells which could be used for regenerative medicine and for treating wounds and burns. The large number of human hereditary hair disorders left to be molecularly defined will provide much fuel for hair follicle based research in the coming years.

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