MINIREVIEW

Molecular Genetics of the Hair Follicle: The State of the Art (44456)

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Abstract. **For those who are interested in the biology of skin and its derivatives, these are interesting times indeed. In a mere 5 years, the field has been revolutionized by the application of molecular genetics to human congenital skin disorders. Where dermatology first was limited to observation and empirics, there are now DNA-diagnostics, rational drug design, and perhaps even gene therapy available soon. In particular, the study of rare human syndromes involving abnormalities of hair growth and structure has yielded new insights into the regulation of cell growth and differentiation in the hair follicle. As this structure shows a cyclic pattern of differentiation, it may give new information concerning the regulation of cell differentiation in general. This review covers the recent developments in this fast-moving field. First, we will give a short introduction to (structural) hair biology. Next, we will try to fit these data into the framework of what is already known and attempt to present a unified model for hair follicle growth and differentiation.** [P.S.E.B.M. 2000, Vol 223]

Biology of the Hair Follicle

Structural Hair Biology. The hair shaft is composed of three different types of epithelial cells: cuticle, cortical, and medullary cells. The inner root sheath (IRS) surrounds the hair shaft and is composed of three cell types as well: the inner root sheath cuticle, Huxley's layer, and Henle's layer. Yet another cellular envelope surrounds the IRS. This is the outer root sheath (ORS), which is composed of two cellular structures. One is the so-called companion layer, and the other consists of ORS cells. This is schematically shown in Figure 1. All cell types except the ORS cells originate from germinal epithelial cells at the base of the hair follicle (1). These cells are in contact with the dermal papilla, which apparently provides nutrients and growth factors. The germinal cells are the only cells, apart from a few ORS cells, that are mitotically active and hence perform DNA synthesis (2). Any hair disorder that results from mutations in genes related to DNA synthesis or transcription will initially affect the germinal layer. Subsequently, it will give rise to abnormalities of all hair layers. Although DNA synthesis ceases when cells leave the germinal epithelium, the mRNA is stable and remains detectable until the keratins in the hair shaft are cross-linked (2).

The synthesis of structural proteins of the hair cortex like hard (or hair-) keratins precedes their assembly into macro-molecular structures. After assembly of the hard keratin complexes, various stabilization mechanisms such as cross-linking by disulfide-bridging result in three-dimensional networks of structural molecules. Two classes of hair keratins are distinguished by high or low sulfur content. There is evidence that these are synthesized in two stages, the low-sulfur proteins being the first to appear (3).

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Schematic representation of a hair follicle

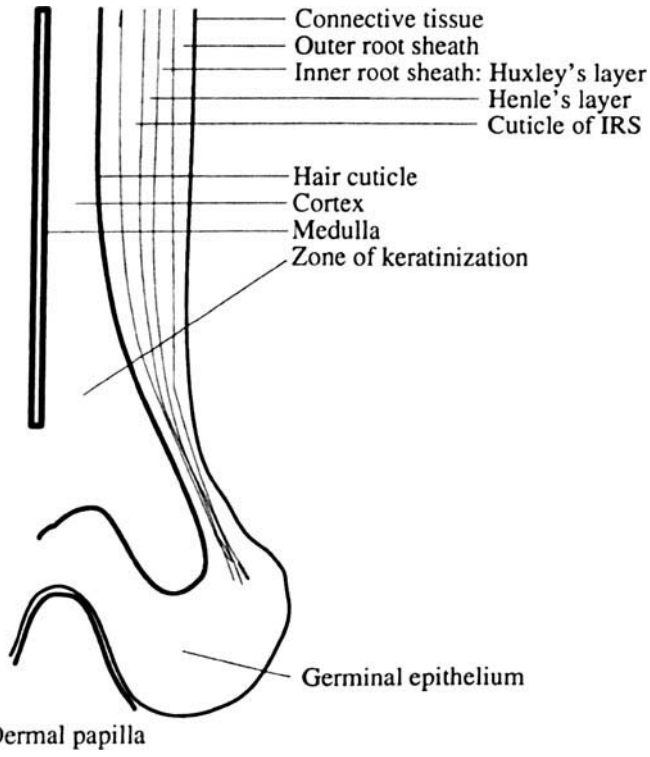

Figure 1. A schematic representation of a human anagen hair follicle. Notice the arrangement of dermal papilla and hair epithelium, resembling the tooth bud in the developing tooth.

Proteins in the cuticle are different from those in the cortex. They form proteinaceous barriers (the so-called exocuticular A-layer) that react with cell membrane remnants. The hydrophobicity of the cuticle results from the presence of long-chain fatty acids, linked through thioester bonds to the underlying proteins that are unique because they contain large amounts of citrulline and are highly acylated. During the initial stages of hair growth, fiber cuticle cells and inner root sheath cuticle cells are in contact with each other. During this phase, intercellular laminae made of fatty acids and protein are formed. Upon extrusion of the hair, pairs of laminae coat the outer surface and form the cuticle (2). In certain aspects, this process is analogous to keratinization in the skin.

Hair Follicle Growth Cycles. Human hair follicles have three distinct growth phases: the anagen (active), catagen (regressive), and telogen (resting) phases. Human hair is cycling asynchronously. In other mammals, such as mice, hair cycling occurs in synchronized waves. This gives rise to the seasonal hair loss known as molting.

During hair growth, 70%–90% of hairs are in the anagen phase (which shortens with age) and may remain there for up to 7 years (2). This period is subject to wide variations, and extremely short anagen phases may lead to apparent alopecia. All hair diseases are actually hair follicle diseases, as hair formation and growth take place in that structure.

Disorders of Hair Growth and Differentiation

So far, our knowledge of hair biology is mainly descriptive and centered on structural proteins. Much of it is derived from the study of wool, which has been studied extensively because of its obvious commercial importance. Very little is known of the genetics of hair growth and differentiation. Recently, some exciting results have given us a glimpse of the mechanisms that control hair follicle growth and differentiation.

In the Beginning—Morphogenesis of Hair Follicles, EDA, and the Wnt Pathway. X-linked hypohidrotic ectodermal dysplasia (Christ-Siemens–Touraine syndrome, MIM 305100) is characterized by abnormal hair and teeth, absent sweat glands, and a peculiar facies. Affected boys cannot sweat, which sometimes leads to life-threatening overheating. Female carriers may show mild abnormalities (usually reduced sweating) in Blaschko's lines, a clinical manifestation of skin mosaicism. *Tabby* is a murine homolog of this disorder.

The locus for Christ-Siemens-Touraine (CST) syndrome was identified in two women manifesting the disorder. They had X-autosome translocations that helped localize the gene to Xq13.1. The responsible gene, called *EDA*, was cloned only recently. The predicted gene product of the *EDA*1 gene isolated by positional cloning is a 135-amino acid protein (isoform I) expressed in hair follicles and in the epidermis of adult skin (4). The protein is predicted to contain a single transmembrane domain, but other functional motifs could not be identified, and the protein was postulated to belong to an entirely new class.

Ferguson *et al.* (5) identified a candidate cDNA for the murine "*Tabby*" (*Ta*) gene, which is the equivalent of *EDA*. Mutations were identified in three different *Ta* alleles, and the gene was found to express at increasing levels during embryogenesis (11–17 days p.c.), the period when ectodermal structures develop and inductive interactions between mesenchymal and ectodermal structures are supposed to take place. The predicted structure of the protein product is similar to a number of membrane-associated proteins with either single or multiple collagenous domains in the extracellular C-terminal regions. Ferguson *et al.* (6) speculated that, since mutations can be identified in only 10%–15% of families with CST, it is likely that additional homologous exons exist for the human *EDA* gene. Indeed, the same authors identified an isoform of the EDA protein in humans. This protein contains seven new exons and is 94% identical to the mouse homolog. Again, it includes the 19-mer extracellular collagen-like domain. Monreal *et al.* (6) identified putative mutations in ≈ 95% of the CST families they investigated. The results suggested that EDA isoform II plays a critical role in tooth, hair, and sweat gland morphogenesis, whereas the biologic significance of isoform I remains unclear.

Remarkably, recent data suggest that EDA may have a function in the regulation of another pathway that has re-

cently been discovered to play a vital role in the morphogenesis of hair follicles.

Wingless and Hair Growth: A Possible Role for EDA? The *Wingless* (or *Wnt* in mammals) pathway, perhaps best known for its involvement in tumorigenesis and Drosophila wing patterning, also seems to be involved in hair follicle development and differentiation (7, 8). The first indication of this was the phenotype of the *Lef1* knockout mouse. *Lef1*, a member of the TCF/LEF/Pangolin family of transcription factors, is bound by β-catenin (an *Armadillo* homolog) and in this complex activates transcription of various downstream genes in response to a WNT protein binding its receptor, Frizzled (Frz) (9, 10). The homozygous knockout mutants lack whisker follicles, body hair, teeth, and mammary glands. The number of follicles is greatly reduced, and those that are present are arrested in their development (11). As may be expected from this phenotype, β-catenin was recently shown to play an important role in hair follicle formation as well. Gat *et al.* (12) generated transgenic mice expressing a β-catenin lacking the N-terminal *GSK3/Zw3* phosphorylation sites in their skins. Abolishment of these phosphorylation sites probably leads to accumulation of β-catenin in the cell, which in turn disrupts the normal functioning of the *Wnt* pathway. In these transgenic mice, *de novo* formation of hair follicles took place throughout life. The new follicles formed sebaceous glands and dermal papillae as well, something that normally occurs only during embryogenesis. The transgenic follicles induced *Lef1* expression, like normal hair follicles. In normal hair follicles, *Sonic Hedgehog* (*Shh*) is expressed during embryogenesis in a polarized pattern and is apparently required for proliferation as well as for organization of the pattern of hair growth (13). Through *Engrailed-1* expression it can also antagonize WNT signaling and thus regulate the placement of hairs over the body surface (which is probably why we have no hairs in the palms of our hands). In β-catenin transgenic follicles, polarization was abolished and growth was disoriented. Additionally, proliferation continued unchecked, resulting in the formation of trichofolliculomas and pilomatricomas, two types of tumors also occurring in humans. Pilomatricomas can be a component of Gardner's syndrome (MIM 175100), which is caused by mutations in the *APC* gene (14). This is a major component of the *Wnt* signaling pathway, being involved in the regulation of β-catenin levels. Thus, a pathway emerges wherein the *Wnt* pathway induces the differentiation of hair follicles and regulates their subsequent proliferation. A tentative model is presented in Figure 2.

In this model, EGF influences E-cadherin function through an Src-kinase (15). Since E-cadherin may be able to downregulate the levels of β-catenin, it is tempting to speculate that EGF secretion by the dermal papilla modifies formation of hair follicles by the epidermis by interacting with the *Wnt* pathway (16). The Egf-receptor knockout mouse has, among other epithelial abnormalities, a reduced number of hair follicles. These are rudimentary and disoriented. This resembles the *Lef1*-knockout phenotype, supporting the notion that EGF interacts with the *Wnt* pathway. The disorientation of hair follicles suggests that the Wingless route may be involved in the phenotype. The CST phenotype bears a close resemblance to core symptoms of the *Lef1* knockout and the *Egfr*-knockout mouse. In our view, this suggests a role for EDA in the regulation of EGF signaling. Also, recent data indicate that there is an interaction between the EDA protein and EGF during normal skin development (17). It is possible that EDA, as a putative transmembrane protein, activates EGFR signal transduction by binding to an as yet unknown EDA ligand on neighboring cells. EDA has significant homology to the globular domain of C1q and Speract receptor proteins (MOTIF search result, unpublished). This suggests that the *EDA* gene may code for a receptor.

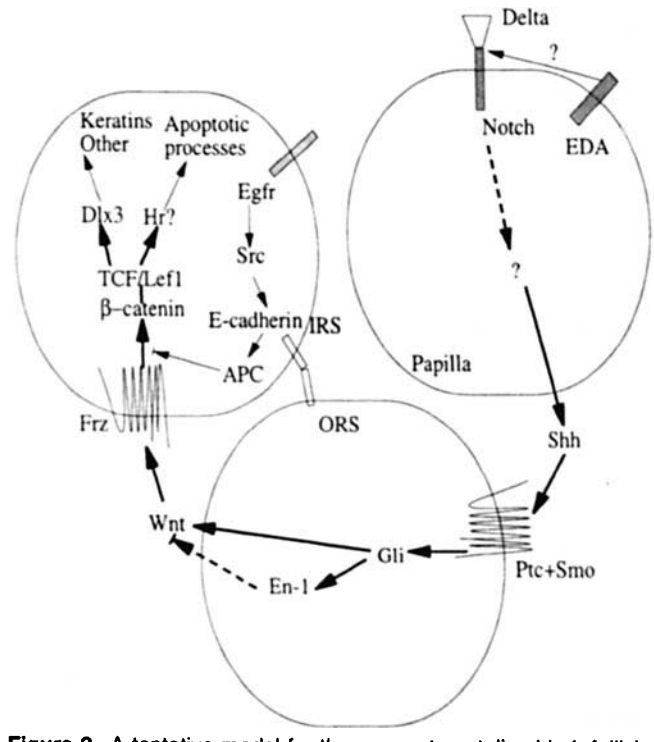

Figure 2. A tentative model for the compartmentalized hair follicle. The signaling cascade runs from papilla to outer root sheath (ORS) and then to the inner root sheath (IRS). The Delta-Notch pathway is proposed to function in the initiation of hair follicle differentiation and to be influenced by EDA. Genes are placed where they are proposed to exert their main effects, although they may be expressed elsewhere. EDA: ectodysplasin; Gli: human glioma transcription factor (homolog of cubitus interruptus); Shh: Sonic hedgehog; Ptc: Patched1 Sonic hedgehog receptor; Smo: Smoothened transmembrane protein; En-1: Engrailed-1; Wnt: Wingless homologs; Frz: Frizzled wnt receptor; TCF/Lef1: lymphoid enhancer factor/pangolin family transcription factor; Dlx3: Distal-less homolog 3; Hr: Hairless; Egfr: epidermal growth factor receptor; Src: Src kinase; APC: Adenomatous polyposis coli gene.

Hairless Humans, Mice, and Flies: Transcription Factors, Apoptosis, and Hair Growth. The rare autosomal recessive disorder atrichia universalis (MIM

203655) is characterized by a complete lack of terminal hairs on the body. Very few hair follicles are present, and those that can be found are dilated and contain either a keratinous plug or no hair at all (18). Recently, Ahmad *et al.* as well as Cichon *et al.* described Pakistani families with this phenotype (18, 19). Upon birth, affected children have scalp hair. This never returns upon ritual shaving, which is usually performed a week after birth. In other words, molting does not take place. They showed that this phenotype is caused by mutations in the human homolog of the mouse *Hairless* gene, mutations of which cause a similar phenotype in mice, as was proposed by J. Sundberg nearly 10 years ago (20). The gene contains a single zinc finger, suggesting that it might function as a transcription factor. Conceptual translation of the cDNA sequence and subsequent PREDATOR and PRODOM 2D-modeling (unpublished results) indicate the presence of some α-helical and collagenous domains. It is conceivable that these are involved in binding the protein to the cytoskeleton. As exemplified by E-cadherin (see above), the cytoskeleton plays an important role in the regulation of transcription.

The murine *Hairless (Hr)* phenotype is almost identical to human atrichia universalis. In *Hairless* mice, hair loss typically begins around the time when the hair follicles enter their cycles of regression (catagen), resting (telogen), and growth (anagen), that is, at first molt. The previously normal-appearing hair follicles disintegrate and leave cysts in the skin (21). This suggests that *Hr* is involved in the initiation of the first telogen-catagen tranformation. Detailed analysis of the mouse phenotype was recently performed by Panteleyev *et al.* (22). It seems that the *Hr* mutation disrupts key functional units in the hair follicle, as the typical Hr cysts are formed from surviving parts of the ORS. The remainder of the hair follicles disappear. The absence of inflammatory reactions suggests that this happens in an apoptotic process.

The *Hr* gene product is obviously required for the passing of the hair follicle from catagen to anagen. In this phase, hairs are shed. This entails downregulation and breakdown of adhesive molecules in the root-sheath (22). At the same time, the ORS cells must reorganize to start the next phase of synthesizing keratins and other structural proteins. It is tempting to speculate that tight regulation of apoptosis is essential for this process and that the absence of hairless somehow leads to aberrant cell death, retention of hair, and cyst formation. This hypothesis is consistent with recent data indicating that apoptosis is important for all phases of hair growth but is especially prominent in cells starting to go catagen. Dysregulation of apoptosis in cultured hair follicles by stimulation with TNFα leads to disruption of normal hair follicle morphology with subsequent loss of the hair (23).

Homeobox Genes and Curly Hair. The genetic pathways described above exert their influence on hair growth mainly by activating other transcription factors. Most of these are presently unknown. However, recent results have identified a rather unexpected transcription factor as an important regulator of hair differentiation. Considering its family affiliation, it is probably downstream of the more general regulators described above. Interestingly, these results also show that the similarities between hair and teeth are not limited to tissue organization but extend down to the genetic level.

Tricho-dento-osseous syndrome (TDO, MIM 190320) is an autosomal dominant disorder characterized by abnormalities of hair, skin, and bone. The main manifestations are taurodontism, enamel hypoplasia, kinky and curly hair at birth, and an increased thickness and density of the cranial bones (24). In mice, it has been demonstrated that mutations in *Dlx* (homologous to the Drosophila gene *Distal-less*) homeobox genes can lead to abnormal development of craniofacial bones and teeth (25). Because of this, genes of the *Dlx* family are attractive candidates for human syndromes with abnormalities of the face and teeth, such as TDO. Indeed, Price *et al.* recently found that the TDO locus contains two human *DLX* genes, *DLX3* and *DLX7*. Subsequently, mutations in *DLX3* were found in TDO syndrome patients (26). The mutations were found to be 4 base-pair deletions in the 3′ ends resulting in frameshifts and premature stops in all cases. The homeodomains are left intact by these deletions, but obviously the 3′ end of the protein is vital for its function. The dominant phenotype suggests that the proteins need to (homo-)dimerize to function correctly. Apparently, this class of homeobox genes is essential for inductive interactions between tissues from different germ layers.

In mice, whiskers and hair follicles strongly express *Dlx3* before birth, followed by a decrease afterwards. Perhaps this correlates with the kinky, curly hair seen in TDO patients at birth. Considering the expression of *Dlx3* in both the mesenchymal and epithelial parts of the developing tooth, it may be expected that it is expressed in the mesenchymal (dermal papilla) and ectodermal parts (germinal epithelium) of the developing hair as well. The similarity in structure of hair and teeth suggests this as well. The hair abnormality in TDO is limited to the outer root sheath. This implies that *DLX3* is required for the transduction of a signal from the dermal papilla to the germinal epithelium that forms the outer root sheath. The nature of this signal is currently not clear.

These findings show that genes whose ancestors are involved in making terminal appendages in fruit flies are actually making terminal skin appendages in mammals. Moreover, this is the first time that homeobox-containing genes have actually been implied in ectodermal-mesenchymal interactions in systems other than the developing limb.

Wavy Hair and Fibroblast Growth Factors. In mice as in humans, a wide variety in hair textures can be found. The extremes of hair texture are labeled as mutants that are usually perpetuated or stored. As a consequence, finding the causes of hair texture variation in mice is easier than in humans. A particularly interesting mutant is *Angora*

(this variation also occurs in cats). Hebert *et al.* (1994) found that mice homozygous for a null allele of the *Fgf5* gene, produced by gene targeting in embryonic stem cells, have abnormally long hair (27). This phenotype is identical to that of homozygous *Angora* (*go*) mice. The transgenic mutant and the "*go*" mutant failed to complement one another, and exon 1 of *Fgf5* was found to be deleted in DNA from *go* homozygotes. Expression of *Fgf5* is detected in wild-type hair follicles and is localized to the outer root sheath during the late anagen phase of the hair growth cycle. It seems that *Fgf5* in one way or another regulates the length of the anagen phase. *Fgf*-receptors 1–3 are involved in the regulation of skeletal growth in vertebrates. In particular, null mutant alleles of *Fgfr3* cause skeletal overgrowth in mice (28). It is tempting to speculate that *Fgf*'s, regardless of their physical localization, have negative regulation of cell growth and differentiation as one of their primary functions. *Fgf3*, for instance, is also known as an oncogene in mouse mammary tumors (29). In that case, it is conceivable that activating *Fgf5* mutations may cause hypotrichosis through shortening of the anagen phase. The phenotype of the *Angora* mutant certainly suggests that *Fgf5* may be responsible for at least part of the normal variation in human hair length.

Epidermal and Keratinocyte Growth Factors: Another Link to the Outside World. Ultimately, the transcription factors that regulate cell differentiation need to be activated by an external signal. Fibroblast growth factors have been mentioned, but little is presently known about their downstream targets. For some other growth factors that have already been mentioned briefly, more data are available.

The keratinocyte growth factor KGF is also known as fibroblast growth factor 7. Given this family affiliation, it will come as no surprise that KGF affects hair texture. In *Kgf* –/– mice, the hair coat develops a somewhat greasy or matted appearance, particularly among male mutant mice. This is not due to oils or grease. The rough nature of the hair coat becomes more prominent with age. By 1 year, females also display the phenotype. In scanning electron micrographs, the hair does not show major surface abnormalities. Moreover, the relative populations of different hair types remain unaffected. The most striking difference in the hairs seems to be a perturbation in the direction of the hairs within the fur coat, which gave the hair coat an unkempt appearance (30). *Kgf* null mice bear a strong resemblance to the recessive mouse mutant *rough* (*ro*) described more than 40 years ago (31). This mutant also has a greasy and rough appearance of the hair coat. It is of interest to note that the abnormalities of the fur in these mice are almost the opposite of the hair phenotype of the *Angora* mutant, that has long, shiny, waved hairs. The downstream components of the KGF route are unknown.

The epidermal growth factor EGF has already been mentioned in conjunction with the *Wnt* pathway. EGF signaling has been most intensively studied in Drosophila, but is seems that here, as in so many other signaling cascades, most players and interactions have been conserved between insects and vertebrates. The importance of the EGF receptor is illustrated by the severity of the resulting mouse phenotype. Unfortunately, a mouse knockout model for EGF itself does not exist, so there is at present no way of knowing whether EGFR accepts other ligands than EGF or whether EGF binds other receptors as well.

Assorted New Findings: Mapping of Defects and Structural Molecules Involved in Hair Loss. Of course, the above discussion covers only a selection of what is new in the field of hair follicle genetics and discusses signaling events during development. Structural molecules, though only briefly mentioned, also play a vital role in the development and maintenance of the hair follicle. We will briefly mention some recent findings.

The intuitive notion that hair keratins must be involved in some hair disease has recently been confirmed by the first reports of hard keratin defects in the dominant hair disorder monilethrix (32, 33). Culprits are the so-called "hard," or hair keratins *hHb6* and *hHb1*. In four unrelated families, helix termination motif mutations in both keratins were identified. These mutations act in a dominant negative way to disturb the assembly of keratin filaments. The scarring alopecia that is part of the phenotype indicates that the hard keratins not only form the cuticle of the hair but are also involved in the structural integrity of the hair follicle itself. By what mechanism this comes about remains to be determined. Perhaps the hard keratins interact, like soft keratins elsewhere in the body, with intracellular adhesion molecules. One of these, *Plakophilin-1*, which is part of the desmomosome, has been shown to be mutated in the ectodermal dysplasia-skin fragility syndrome (34, 35). Interestingly, one of the features of this syndrome is scarring alopecia. Since Plakophilin-1 has been shown to interact with epidermal keratins (36), it is tempting to speculate that hair keratins also bind to plakophilin and thus contribute to the structural integrity of the hair follicle itself. Plakophilin-1, a member of the Cadherin family, has a close relative, Plakophilin-3. The latter has been shown to have a nuclear as well as cytoplasmic localization (37). This, together with the *Armadillo* repeats that the plakophilins contain, suggests a role in transcription. The ectodermal dysplasia-skin fragility phenotype also suggests a role for Plakophilin-1 beyond being part of the cytoskeleton (32). Thus, structural molecules may exert influence over transcription in the hair follicle by means of their association with desmosomal proteins.

Complex Signaling in the Hair Follicle. With the above data, a tentative model of the genetic pathways in the hair follicle may be presented. Though woefully incomplete, some of the genes that are known to function in hair development may be placed in a signaling cascade that ultimately initiates hair growth, that is, induces hair follicle cells to pass from the catagen to the anagen phase. This model is presented in Figure 2 and shows a tentative genetic

pathway. The inner root sheath (IRS) and outer root sheath (ORS) cells are considered different functional compartments. The same goes for the ORS itself, but since it is not clear what distinguishes these, the ORS is modelled as a single structure. The IRS functions as an intermediate between the dermal papilla, that initiates hair growth and its cycles, and the ORS, that executes a large part of the final elaboration of the hair structure. In this view, the dermal papilla functions as a kind of master regulator of the hair cycle. Programmed cell death is likely to be of importance in the cycles of growth and regression that take place during normal hair growth. Though it is not known at present how this is regulated, the hairless phenotype suggests that apoptosis is vital for hair growth during the first molt, that is prior to terminal differentiation of the hair.

Hair growth starts with an ectodermal placode that is probably differentiated from the rest of the skin under influence of *Delta-Notch* signaling. Once the initial structures are in position, the WNT pathway, together with Sonic Hedgehog (*Shh*), is responsible for initial differentiation and proliferation of hair. Asymmetric expression of *Shh* polarizes the hair, ensuring that outgrowth of hairs in a defined area is in a single direction. Through Engrailed-1, certain areas of the body are kept free of terminal hairs whereas other areas, under the influence of WNT proteins, do grow them. The first "real," or terminal hairs start to grow shortly after birth, in response to an as yet unknown signal that may be hormonal in nature. This signal triggers the cascade that is presented in Figure 2 and that functions throughout life in the regulation of hair growth. How structural molecules relate to these events is presently unclear.

The cascades that initiate hair follicle growth probably do not become inactive, since many men acquire additional terminal body hair during life. It is possible that they control hair follicle cycling in adults. Thus the hair follicle is a complicated structure where complex gene interactions regulate growth. The hair follicle can relatively easily be isolated for study and can as such be an important model system for other structures that depend on ectodermal-mesenchymal interactions.

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