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Normal Variation in Human Hair Production

The mammalian hair follicle is a dynamic structure that generates a hair shaft through a tightly controlled cycle of growth, remodeling, and loss. Once a hair follicle is made, it can undergo many of these cycles, continually making, growing, and losing the hair shaft. In mammals, the cycle of hair growth includes three stages: anagen (follicle generation and hair production), catagen (follicle regression), and telogen (resting phase). A commercial site describes this cycle of hair regeneration.

The production of the follicle is an extremely complicated event, and literally dozens of genes are known to play roles in its formation. We can only discuss a few of them here. Like the kidney, tooth, and the eye, there are reciprocal inductions. In this case, the developmental dialogue involves the epidermal cells of the skin (an ectodermal epithelium) and the dermal cells beneath it (a mesodermal mesenchyme). The progression of the developmental dialogue for hair formation has been summarized by Philpott and Paus (1998) and Müller-Röver and Paus (1998).

Initial inductive events

- The first signal is probably from the dermis, telling the epidermis to “make an appendage.” Regions of epidermal cells proliferate and form local thickenings (placodes) of the epidermis. The signal here may be TGF-b molecules. The epidermis thickens in these regions and expresses particular adhesion molecules such as NCAM. These adhesion molecules are thought to separate the presumptive follicle cells from the remainder of the epidermis.
- The epidermal placodes then respond by sending a message into the mesenchyme, telling the mesenchyme cells to “aggregate beneath the epidermal placodes.” This signal appears to be a series of paracrine factors including fibroblast growth factors, sonic hedgehog, and BMP2.
- Once aggregated, these mesenchyme cells now form the dermal papilla. The papilla sends a second message to the epidermis: “make a hair placode.”
- The epidermis responds to this signal by proliferating further into the mesenchyme. As it does so, it sends a signal to the mesenchyme, signaling the mesenchyme to condense into the definitive dermal papilla that will become surrounded by the proliferating epidermal placode. The epidermal placode has now become a primitive hair shaft.

These events are summarized on a commercial website for hair growth products.

Differentiation of the hair shaft

The next stages involve the differentiation of the hair shaft. The epidermal hair germ is surrounded by mesoderm. At its base is the dermal papilla. On its sides are less condensed mesenchyme, which, nevertheless, had been part of the original dermal papilla. During anagen, pluripotent epidermal matrix cells in the hair bulb move upward. Their cell fate is specified by their initial positioning relative to the dermal papilla at the base of the follicle (Chase, 1954; Millar et al., 1999). Cells at the center of the follicle become the medulla (center) of the hair shaft, while slightly more marginal cells become the cortex and cuticle of the hair shaft. Even more peripheral cells, those cells

differentiating at the base of the dermal papilla (near where it meets the tip of the ectoderm), differentiate into the inner root sheath.

- The regions of the hair peg become distinguishable by their cell adhesion molecules. Therefore, the hair follicle is being divided into functional groups of cells. The dermal papilla is characterized by NCAM expression. The innermost region of the hair matrix, directly atop the dermal papilla is characterized by P cadherin, while the region above that has both E and P cadherin. This will become the keratogenic hair matrix. The outermost hair matrix contains E cadherin.
- Melanin pigment from the neural crest melanoblast cells enters into the hair shaft, mingling with the keratogenic hair matrix cells. At the same time, sebocytes, the precursors of the sebaceous gland cells, differentiate near the junction of the hair peg and the skin.
- The sebocytes form two bulges. The uppermost bulge becomes the sebaceous gland, while the lower bulge becomes the attachment site for the arrector pili muscles (those that “make your hair stand on end”) and the residence of the hair follicle stem cells. In the armpit and perianal regions, a third bulge will form, and this will become the apocrine sweat gland.
- The innermost regions of the hair peg become the cortex and cuticle of the hair fiber, while the outer layers become parts of the inner root sheath that covers the hair shaft. As a result of continued proliferation by the stem cells directly over the dermal papilla, the hair fiber is pushed upwards within the follicle and it produces the hair keratins. The hair shaft then extends through the hair canal, an opening that is thought to be formed by the apoptosis of the cells at the center of the hair peg where the hair peg meets the skin.
- The outer root sheath surrounds the hair follicle (much like a sleeve) and it is continuous with the epidermis. It has two proliferation zones: (1) in the bulb and (2) in the basal layer of the epidermis. In the bulb, there are two layers. The outer layer of the cell is germinative and continuous with the epidermal basal cells. Differentiation occurs by the horizontal movements of cells from the basal layer of the outer root sheath to the center of the follicle.

Hair placement and growth

It is not known why certain regions of the body are allowed to have hair and other regions are not. It is also not known why the hair on our scalp and chin is allowed to grow continuously and become long, while our armpit hair, eyebrows, and pubic hair never grow past a certain length. The regionalization of the dermis may have something to do with this, but what the dermis does is not known.

Hypertrichosis

However, there are some individuals whose hair growth and placement are genetically altered. A striking (at least to us humans) mutation involving hair growth is congenital generalized hypertrichosis. This very rare X-linked dominant condition is characterized by excessive facial and upper torso hair in males and by a less severe asymmetric hairiness in females. The people who have this condition have hair placement more typical of mammals in general, and less typical of the human hair placement. (Indeed, it has led to such people being exhibited in side-shows as “dog man,” “the human terrier,” “werewolf” and other such designations.) Figuera and colleagues (1995) have been mapping this gene and showed that it is on the long arm of the X chromosome, between Xq24-Xq27. This is the first example of a gene that may be involved in the regulation of human hair growth to certain regions of the body.

FGF5. In mice, the coat hair has a genetically defined length. (Mice don't need haircuts). This length can be altered by the *angora* mutation. The angora mouse mutant has abnormally long hair, due to

an increase in the time that the follicles remain in the anagen phase of this cycle (Pennycuik and Raphael, 1984). This condition is due to mutations in the gene for fibroblast growth factor 5 (FGF5), which is expressed in the outer root sheath of the hair follicle (Hébert et al., 1994). FGF-5 appears to be needed for the progression of the hair cycle from the anagen stage to the catagen stage. Without FGF-5, this time is delayed and the hair shaft keeps growing. Eventually, the catagenic stage is reached, perhaps because the hair matrix cells have only a limited capacity for proliferation or perhaps because another FGF molecule can substitute at a lower efficiency.

WNT3. The paracrine factor Wnt3 may also be involved in regulating the limits of hair growth. Wnt3 is expressed (in both developing and mature hair follicles) in the matrix cells that will become the medulla of the hair shaft. Overexpression of *Wnt3* in transgenic mouse skin causes a short-hair phenotype (Millar et al., 1999). This shortening of the hair is caused by the altered differentiation of hair shaft precursor cells. A putative effector molecule for WNT3 signaling, the cytoplasmic protein Dishevelled-2, is normally present at high levels in a subset of cells in the outer root sheath and in precursor cells of the hair shaft cortex and cuticle which lie immediately to the lateral sides of the *Wnt3*-expressing cells. Overexpression of Dishevelled-2 in the outer root sheath mimics the short-hair phenotype produced by overexpression of Wnt3.

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