Hair follicle structure and function

CD Milley

Animal Dermatology Clinic Portland, Portland, OR, USA

HAIR AND HAIR FOLLICLE FUNCTION

- Thermoregulation
  - Insulation
  - Dependent on length, thickness, density/ unit area, medullation
  - Piloerection increases coat depth
  - Gloss reflects sunlight
- Physical protection
  - Barrier against chemical, physical and microbial insults
- Sensory perception and tactile activity
- Social interactions
  - Hold scent
  - Piloerection
- Dispersion of sweat and sebum
- Water repellency
- Hair pigmentation essential to proper hair function
  - Thermoregulation
  - Camouflage
  - UV protection
  - Sexual signaling

EMBRYOLOGY

Most hair follicles develop before birth. An exception to this is marsupials in whom hair follicle plugs (hair placode/ hair germ) are seen after birth (marsupials are born at a very immature stage of development and further develop in the pouch). In dogs, secondary hair follicles don't develop until after birth (ie- dogs gain an adult coat rather than loose a puppy coat).

Hair follicle development in the fetus is dependent on interactions between the ectoderm and the mesoderm. Ectodermal derived tissues include all the epithelial components of the hair follicle, the sebaceous, and apocrine glands which develop from hair follicle stem cells. The mesoderm forms the hair papilla and connective tissue sheath. The pigmentary unit is formed from melanocyte progenitors which originate in the neural crest.

The first follicles to develop are the vibrissae and tactile/ sinus hairs on the chin, eyebrow and upper lip. Body hair follicle development then begins on the head and moves downward. Hair follicle development has been divided into 8 stages, each of which has its own expression of signaling molecules. The genes and signaling molecules involved in hair follicle development are also involved in hair follicle cycling in the adult animal. The first step in follicle development is the formation of an epithelial placode (hair placode/ hair germ) which is a collection of epithelial cells and the formation of a mesenchymal condensation in the dermis. Wnt (wingless)

signaling is essential for this initial step to occur. The hair placode develops into a hair peg/ hair bud which eventually elongates and differentiates into a fully formed hair follicle. The mesenchymal condensation develops into the dermal papilla. Both hair follicle elongation and dermal papilla development are mediated by Shh (Sonic hedgehog) signaling. As the hair peg elongates it also broadens. The deepest portion becomes bulb-like and surrounds the dermal papilla and will eventually become the hair follicle matrix. The ORS (outer root sheath) of the hair peg develops 3 bulges at the cranial edge of primary follicles and at the caudal edge of secondary follicles. These bulges correspond to the attachment of the arrector pili muscle, the sebaceous gland and the epitrichial sweat gland (from deep to superficial).

Important genes involved in hair follicle development and structure:

- Homeobox genes
    - Responsible for nonrandom, symmetrical distribution of hair follicles
- FGF-5 gene
    - Responsible for hair length
- Keratin-71 gene
    - Responsible for hair curl
- R-spondin 2 gene
    - Responsible for hair size/ texture

Some of the important molecular signals in hair follicle formation include:

- Wnt (wingless)/ β-catenin pathway
    - "Master switch", required for hair follicle induction and initial placode development
    - Originates from the epidermal cells
        - Determines differentiation into hair follicle keratinocytes
    - Required to induce anagen along with BMP antagonists (eg- noggin) and Shh in the mature follicle
    - β-catenin = downstream mediator of Wnt signaling
        - Translocates to the nucleus and is responsible for homeobox gene signaling
            - Interacts with Lef-1 (transcription factor)
        - Constant activation results in pliomatricomas and trichofolliculomas
    - Responsible for hair shaft formation
- Shh (Sonic hedgehog)
    - Essential for dermal papilla maturation
    - Responsible for elongation of the hair germ via epithelial cell proliferation and lateral expansion of the follicular placode
    - Anagen inducer in mature follicles
    - Autocrine and paracrine functionality
        - Secreted from both hair germ cells and dermal papilla
- TGF- family proteins
    - BMP

        - Member of TGF-β family
        - Essential for differentiation of the IRS and hair shaft
        - Inhibits follicle and placode development
        - Catagen induction in mature follicle
        - Noggin = BMP antagonist
            - Anagen inducer in mature follicle
            - Increases Lef-1 expression
    - TGF-α/ EGF
        - Ligand from EGFR
        - Catagen induction in the mature follicle
- FGF5
    - Catagen inducer in the mature follicle
    - Deficiency results in angora hair type (long anagen)
- EDA/ EDAR
    - Essential for the development of multiple ectodermal tissues (hair, teeth, glands)
    - Promotes hair follicle development at the placode level
    - Downstream mediator of Wnt signaling
    - Gene mutations result in X-linked ectodermal dysplasia

ANATOMY

Glossary (adapted from Schneider et al, 2009):

Arrector pili muscle	Smooth muscle that connects hair follicle with the dermis. When contracted, causes hair raising
Bulb	Thickening of the proximal end of the hair follicle. Contains rapidly proliferating, undifferentiated matrix cells, melanocytes, and ORS cells
Bulge	Insertion site of the arrector pili muscle. Contains hair follicle stem cells. **Not specifically present in dogs**
Club hair	Fully keratinized hair present during telogen and catagen
Dermal papilla	Mesodermal signaling center of the hair follicle. Contains fibroblasts. Continuous with dermal connective tissue. Aaro-Perkins corpuscle below; hair matrix above.
Hair shaft	The hair, composed of terminally differentiated hair follicle keratinocytes. Central medulla, outer cortex, melanin granules (most important in the cortex for coloration), and hair cuticle
Inferior segment	Most distal portion of the follicle relative to the epidermis. Extends from the bulge/ arrector pili attachment to the bulb. Cycling portion of the hair follicle (ie- not always present). Also called the suprabulbar region.
Infundibulum	Proximal portion of the follicle relative to the epidermis. Extends from the sebaceous duct to the epidermal surface.
Inner root sheath (IRS)	Rigid tube composed of terminally differentiated hair follicle keratinocytes, surrounded by ORS. Layers (from inside- out): IRS cuticle, Huxley, Henle, companion.
Isthmus	Middle part of the follicle. Extends from the bulge/ arrector pili attachment to the sebaceous duct.

Outer root sheath (ORS)	Outermost layer of follicle. Proximally, merges with the basal layer of the epidermis; distally merges with the hair bulb

Hair types

Most hairs in companion animals are medullated. Medullated hairs can be primary (outer or guard hairs) or secondary (undercoat, down hairs). Secondary hairs do not usually have an epitrichial sweat gland associated with them. Nonmedullated hairs form the wool of sheep and angora goats and most of the hairs in Sphinx cats. Other nonmedullated hairs include the vellus hairs in humans (the fine hairs on the face and arms) and lanugo hairs which are present in the prenatal period. Hair follicles may be simple (containing only 1 hair) or compound (containing multiple hairs). Most omnivores and herbivores have simple follicles, although telogen hairs may be retained when the new anagen hair forms making these follicles appear similar to compound follicles. Carnivores (dogs and cats), rabbits, and sheep have compound follicles so that multiple (3-20) secondary hair follicles join with a primary hair follicle and have a singular infundibulum. Chinchillas may have up to 60 hairs/ follicle. Dogs are born with simple follicles that develop into compound follicles when the secondary hair follicles form in the first 12-28 weeks of life. The shape and size of the hair is determined by the shape and size of the follicle (i.e.- curly follicles produce curly hairs, large follicles product large hairs).

Besides pelage hair, there are 2 types of tactile hairs in mammals. The sinus hairs (vibrissae/ whiskers) are found on the muzzle, lip, eyelid, face, throat, and palmar carpus in cats. These hairs are thick, stiff, and tapered. They are surrounded by a blood-filled sinus between the ORS and the connective tissue capsule. The sinus has a superior non-trabecular ring and an inferior trabecular/ cavernous area which contains nerve fibers. A thickened cushion of mesenchyme projects into the non-trabecular sinus called the sinus pad and Pacinian corpuscles are found close to the sinus hairs. Sinus hairs are slow adapting mechanorecptors.

Tylotrich hairs are scattered throughout the pelage. They are simple, large follicles containing a single, stout hair and are surrounded by an annular complex of neurovascular tissue at the level of the sebaceous gland. These hair follicles are associated with tylotrich pads which are a thickened area of epidermis that overlies connective tissue with a high concentration of vessels and nerves. Tylotrich hairs are rapid-adapting mechanoreceptors.

Hair follicle sections

The infundibulum and isthmus are part of the “permanent” follicular structure. The inferior segment is only present during anagen when the hair follicle is actively cycling and producing a hair shaft and catagen when the hair follicle is regressing. The outermost layer of the follicular structure is the fibrous connective tissue sheath which is composed primarily of type III collagen.

Outer root sheath

Just inside the fibrous connective tissue sheath is the ORS. The ORS is thickest near the epidermis and thinnest near the bulb where it is a single layer of flattened cells. The cells in the inferior segment of the ORS just above the bulb are large and contain glycogen so that their

cytoplasm is clear and vacuolated. In the isthmus, the inner most cells of the ORS undergo trichilemmal keratinization (without the formation of keratohyalin granules/ a granular layer). Trichilemmal keratinization is an abrupt conversion of the non-keratinized ORS cells into anuclear keratin, and it occurs wherever the ORS is not apposed to the IRS. In the infundibulum, the remaining ORS undergoes keratinization in the same way as the epidermis (with the formation of keratohyalin granules/ a granular layer). The ORS contains keratinocyte and melanocyte stem cells needed for follicular cycling. In people and mice these stem cells are concentrated at the bulge region. In dogs, although stem cells are concentrated near the region of the arrector pili attachment, they appear to be more widely distributed throughout the isthmus. A glassy membrane surrounds the outside of the ORS and is an extension of the epidermal basement membrane and continuous with the basement membrane surrounding the dermal papilla. Mineralization of the glassy membrane is seen in healthy toy poodles and Bedlington terriers but is also seen as an aging change in all breeds.

Inner root sheath

The IRS is present from the bulb to the isthmus. It is absent in telogen follicles. The IRS keratinizes and disintegrates at the same level where trichilemmal keratinization begins in the ORS (at the isthmus). The outermost layer of the IRS is the companion layer which acts as a slippage plane between the stationary ORS and the upward moving IRS- it is tightly bound to the Henle layer. The Henle layer is one cell layer thick and is the first layer of the IRS to keratinize. The Huxley layer is 1-4 cells deep and keratinizes above the Henle layer at a region called Adamson's fringe. Adamson's fringe is at the upper margin of the keratogenous zone where the hair shaft is completely cornified. Its clinical significance can be seen in dermatophytosis- dermatophytes typically only infect fully keratinized tissues, so downward invasion of the hair shafts stops at Adamson's fringe. Cells of the Henle and Huxley layers contain trichohyalin granules which are a morphological hallmark of the IRS (and the hair medulla). Trichohyalin granules are the IRS equivalent of keratohyalin granules in the epidermis and function to promote lateral alignment and aggregation of intermediate filaments during keratinization. The inner most layer of the IRS is the cuticle whose cells overlap to a form a "shingled roof" appearance. The free edge of the IRS cuticle cells are angled toward the bulb and interlock precisely with the similarly shaped hair cuticle cells whose "shingles" are angled toward the hair tip. This tight interaction between the IRS and the hair shaft allows the IRS to perform its function of molding the hair since the IRS keratinizes/ hardens in advance of the hair shaft.

Hair shaft

The hair shaft (and IRS) originates from the matrix keratinocytes in the bulb. The cuticle intertwines with the IRS and thus the shape of the hair is dependent on the shape of the follicle. The cortex provides the mechanical strength of the hair and is composed of cornified, spindle shaped cells. Melanin pigment in the cortex determines hair shaft color. The inner most portion of the hair shaft is the medulla which is composed of cuboidal cells. The medulla contains "solid" cells with trichohyalin granules at the base and air and glycogen vacuoles distally. The medulla may or may not contain pigment, but this pigment does not have much influence on hair shaft color.

HAIR PIGMENTATION

Melanin is produced in the anagen bulb and in addition to providing pigment it may also reduce stress from reactive oxygen species (ROS) produced by the highly metabolically active matrix keratinocytes via its action as a potent free-radical scavenger. Melanogenesis is coupled with anagen and is shut off early during the transition to catagen when some melanocytes undergo apoptosis and others drop into the dermal papilla. Melanocytes that produce hair pigment can be found in the hair bulb in anagen follicles. Melanocytic stem cells are maintained in the bulge/ ORS and repopulate the hair matrix during anagen. Two mechanisms of graying are proposed and include depletion of the melanocytic stem cell reservoir with repeated cycling as well as damage to the pigmentary unit via ROS.

Melanin is deposited into hair shaft keratinocytes where it determines hair color. The wild-type/ classic hair color in dogs is agouti which produces a light tip, a heavily pigmented body and a yellow or red base. The wild-type/ classic hair pattern in cats is tabby/ agouti which produces a black tip, yellow banding in the body and a blue base. Normally, melanin granules are small and distributed uniformly throughout a pigmented region of hair. A mutation in the dilution gene in dogs causes large, irregular granule formation with irregular distribution resulting in melanin clumping and hair shaft perturbations which is the cause of color dilution alopecia. Pointed coats in cats are due to a condition called acromelanism. These cats have a temperature dependent enzyme which converts melanin precursors to melanin only in relatively lower temperature areas so that warm areas are lighter in pigment and cool areas are darker.

HAIR CYCLING

There are 3 main phases to hair cycling including anagen (growth phase), catagen (regression), and telogen (resting). Kenogen is an additional phase which describes hairless telogen, and exogen (hair shedding) is considered a separate phase in some instances. Anagen can be divided into 7 stages and catagen can be divided into 8 phases. Hair cycling in animals is generally in a mosaic pattern, however, rabbits and rodents except Guinea pigs cycle in synchronized, orderly waves that starts ventrally between the front legs and progresses dorsally and caudally. Coat length depends on the relative length of anagen- most animals have telogen predominant cycles. Cycling is influenced by morphogens and hormones as well as ambient temperature, general health and nutrition, and genetic influences.

- Early anagen
    - Induction of anagen is dependent on Wnt, noggin and Shh signaling as well as KGF
    - Dermal papilla migrates down a fibrous streamer/ follicular style and becomes enclosed by hair matrix cells
    - Hair matrix cells begin to differentiate into hair shaft and IRS
        - Dependent on Wnt signaling and BMP
    - Melanin production begins in the bulb
- Late anagen

    - Dermal papilla reaches its deepest location and becomes fully enclosed by the bulb/ hair matrix
    - Hair shaft is fully developed and surrounded by IRS
    - Old club hair may still be present but is usually eventually lost (exogen) in late anagen
    - IGF-1 is a potent anagen stimulator
- Early catagen
    - Induction of catagen is dependent on BMP signaling as well as TGF-α, FGF-5, and vitamin D receptor activity
    - Melanogenesis stops and fewer to no melanin granules are visible above the dermal papilla
    - The bulb narrows and mitotic activity stops
    - Dermal papilla changes shape and moves upward
    - Trailing connective tissue sheath becomes visible
- Late catagen
    - Shortened hair follicle
    - Club hair is formed
    - Trailing connective tissue sheath eventually shrinks and disappears
- Telogen
    - Hair follicle and dermal papilla are in the dermis
    - No IRS
    - Club hair anchored in trichilemmal keratin
- Exogen
    - Timing of club hair release variable
- Kenogen
    - Hairless telogen
    - ORS with no hair or cornified debris in the lumen

Hormonal effects on the hair cycle

- Seasonal
    - Photoperiod/ day length is more important than temperature
    - Hypothalamus, hypophysis and pineal gland are stimulated by daylight to produce hormones (melatonin, prolactin, gonadal, thyroidal, adrenocortical) which influence hair cycling
    - Hair growth increases in the summer and decreases in the winter
    - Shedding usually occurs in the spring and fall
        - Similar phenomenon is seen in people but to a lesser extent
        - Spring molt in ferrets can be quite dramatic and result in seasonal alopecia
- Melatonin
    - Decreased production with long daylight periods
    - Melatonin increases the production of prolactin
        - Prolactin inhibits hair shaft elongation and induces catagen in most species
        - In cashmere goats, prolactin induces anagen

    - Melatonin downregulates apoptosis and estrogen receptor expression in hair follicles
    - Free radical scavenger and DNA repair inducer, so may provide protective effects to the metabolically active anagen bulb
    - Influences sex hormone concentrations which can then affect hair cycling
- Thyroid hormones
    - Thyroxine stimulates anagen and stem cell differentiation
        - Hypothyroid dogs have poor follicular activity and an increased number of follicles in telogen
    - T3 and T4 increase melanogenesis in follicles
    - T3 and T4 stimulate the hair matrix and keratinocyte proliferation and downregulate apoptosis thereby inhibiting catagen
- Glucocorticoids/ cortisol
    - Role in hair cycling is not fully understood
    - Reduced synthesis and increased degradation of hyaluronans and proteoglycans needed for follicular function
    - Glucocorticoids suppress anagen
    - Dexamethasone can induce catagen in mice
- Progesterone
    - Poorly defined effects on hair cycling
    - Binds to glucocorticoid receptor in dog and cross-reacts with the testosterone receptor
- Estrogens
    - Shorten anagen, promote catagen, lengthen telogen
        - Opposite effect in people: stimulates scalp hair growth
            - Possibly via anti-androgenic effects or because of differing estrogen receptor expression
    - Stimulates BMP expression
- Androgens
    - Humans: androgens stimulate hair growth everywhere but the eyelashes where they seem to have no effect and the scalp where they inhibit hair growth
        - Scalp hairs become miniaturized with a shortened anagen
        - Effects are exerted at the level of the dermal papilla
            - This is why transplants work
    - Testosterone seems to have minimal effects on canine hair follicle growth
- Spaying/ neutering can affect coat quality in some animals (20%)
    - Woolly coat: increased undercoat, increased curl, dulling of color
    - The pathomechanism is unknown

<u>IMMUNOLOGY</u>

The upper portion of the hair follicle contains a number of antigen presenting Langerhans cells in the ORS. This population can serve as a reserve to repopulate the epidermis. By contrast, the lower portions of the hair follicle exhibit relative immune privilege in a healthy state. There are 2

areas of primary immune privilege including the bulge region/ ORS stem cell population and the anagen hair bulb. This immune privilege is exhibited by an absence of MHC class I expression (partially through the action of melanocytes which work to actively downregulate this signaling molecule) in the follicle below the attachment of the arrector pili muscle. β-2 microglobulin is reduced in expression which leads to a failure to stabilize MHC class I molecules as well. The bulge also has increased expression of the "no danger" signal CD200 and MHC class II expression is reduced significantly in the bulb and partially in the bulge. The extracellular matrix surrounding the hair follicle has a high concentration of glycosaminoglycans which is suspected to impede T-cell trafficking to the follicle as additional insulator.

The hair follicle itself produces immunosuppressive molecules such as TGF-β2 and α-MSH which impair antigen presenting cell function and prevent NK/ CD8+ cell attacks. The anti-inflammatory cytokine IL-10 and MIF (macrophage migration inhibition factor) also work to reduce the effects of the immune system locally.

The collapse of immune privilege causes alopecia areata.

<u>SELECT DISEASES OF THE HAIR FOLLICLE AND HAIR CYCLE</u>

Focus on non-inflammatory, non-endocrine conditions

- Telogen effluvium/ defluxion
    - In humans this condition has been separated into 5 different categories
    - Anagen is terminated prematurely and all hairs enter telogen
    - Telogen hairs are all then shed simultaneously when the follicle re-enters anagen
        - Usually 1-3 months after the inciting incident
    - Inciting events are usually some form of stressor
        - High fever
        - Pregnancy
            - Pregnancy stimulates anagen, when stimulus is removed the follicles enter telogen, so the inciting event is actually birthing
        - Shock
        - Severe illness
        - Surgery
        - Anesthesia
        - Drugs: doxorubicin
    - Substance P may have a role to play
- Anagen effluvium/ defluxion
    - Very uncommon
    - Anagen phase is interrupted and hair is damaged- falls out but the growth phase continues
        - Hair shaft abnormalities can be seen on trichogram
    - Caused by toxins, chemotherapy, other insults
        - Hair loss occurs within days of the insult
- Congenital hypotrichosis/ alopecia

    - Either reduced number of follicles formed in utero OR hair follicles form at normal density but fail to regenerate/ cycle following the 2nd or 3rd catagen
        - May be born without normal hair
        - May have hair loss within the first 6 months of life (usually within the first 4 weeks)
    - Some forms are X-linked
        - Ectodermal dysplasia in dogs, cattle, people due to EDA/EDAR mutations
    - Some forms are autosomal dominant
        - Mexican hairless and Chinese crested
    - Some forms are autosomal recessive
        - Sphynx
    - Additional ectodermal defects may exist
        - Dentition, claws, epitrichial or atrichial sweat glands, lacrimal glands, sebaceous glands, bronchial glands
        - Decreased glandular secretions lead to difficulty thermoregulating, predisposition to respiratory illness, predisposition to corneal abnormalities
- Color linked follicular dysplasias
    - Black hair follicular dysplasia
        - Dogs, cows
        - Disorder of melanosome transfer or migration
            - Disorderly proliferation of hair matrix cells
        - Coat changes usually by 4 weeks of age, only the black haired areas affected
    - Color dilution alopecia
        - Dogs, cats
        - Individuals with blue, fawn or grey/ silver coats
        - Irregular melanin transfer and storage
        - Hair loss is due to shaft fracture
        - Gradual onset, usually by 3 years of age
    - Melanin clumping, macromelanosomes in hair shafts that disturb the cortex and hair shaft structure
    - Follicular lipidosis
        - Mahogany points of face and paws in rottweilers
        - Present within the first year
        - Lipid accumulation in matrix keratinocytes of anagen bulb
- Other follicular dysplasias
    - Often present with increased number of kenogen follicles, sebaceous melanosis, dysplastic follicles, altered hair cycling
    - Typically, bilaterally symmetrical
    - Cyclical and structural forms exist
        - Cyclical: cyclical flank alopecia, post-clipping alopecia, catagen arrest
        - Structural: usually breed related

    - Pattern baldness
        - Hair follicle miniaturization in affected areas
- Alopecia X
    - Plush coated breeds (e.g.- Pomeranian), poodles, Schipperke
    - Bilaterally symmetrical, spares the head and distal limbs
- Structural defects of the hair shaft
    - Trichorrhexis nodosa, trichoptilosis, medullary trichomalacia
        - More commonly acquired due to external insults and damage to the cuticle
        - May be an inherited trait in some animals
    - Pili torti
        - Secondary hairs are flattened and rotated
    - Hair shaft disorder of Abyssinian cats
        - Only affects whiskers and primary hairs
        - Onion-shaped swelling at the tip of the hair
            - Fracture more easily, coat appears rough and lusterless
    - Spiculosis
        - Male Kerry blue terriers
        - Hard, brittle follicular spicules

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