Dermal Papilla: Molecular Signaling

Essay

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List of abbreviations

ACTßA.....Activin ßa
AMPs .....Acid mucopolysaccharides
Apaf-1 .....Apoptotic peptidase activating factor 1
APC .....Adenomatous polyposis coli
BCC .....Basal cell carcinoma
BMP .....Bone morphogenic protein
Cq1 .....The complement component Cq1
DP.....Dermal papilla
DSH .....Disheveled family protein
EDA .....Ectodysplasin
EDAR.....Ectodysplasin receptor
EGF .....Epidermal growth factor
E-M .....Epithelial-mesenchymal interactions
FGF .....Fibroblast growth factor
FS ..... Follistatin
FZD .....Frizzled
GLI3..... Cubitus interruptus homologue
GSK.....Glycogen synthetase kinase
HF.....Hair follicle
HGF.....Hepatocyte growth factor
HoxC13..... Homeobox cluster gene
HR .....Hairless protein
HS.....Hair shaft
IAP .....The inhibitor of apoptosis protein
IFN .....Interferon
IRS .....Inner root sheath
KC .....Keratinocytes
KO.....Knockout
KZ .....Keratogenous zone

LEF-1 .....lymphoid enchancer factor-1
NBCCS.....Nevoid basal cell carcinoma syndrome
ORS .....Outer root sheath
PAS .....Periodic-acid-Schiff
PDGF-A .....Platelet-derived growth factor-A
PTCH1 .....Patched 1
r .....Receptor
SHH.....Sonic hedgehog
SMOH .....Smoothened
TCF .....T cell factor
TGF .....Transforming growth factor
TGF .....Transforming growth factor
TNF .....Tumor necrosis factor
Wc .....Waved coat
Whn .....Winged helix nude
WNT .....Wingless intercellular signaling protein

Introduction

Knowledge of the molecules and pathways that regulate hair follicle formation and hair growth is essential for achieving therapeutic goals for hair loss conditions, including the ability to create new hair follicles, to change the characteristics such as size or shape of existing follicles and to alter hair growth in existing follicles***(Cotsarelis and Millar, 2001).*** Inhibiting the activities of molecules important for hair follicle formation and cyclical growth may also ultimately provide us with means for treating hirsutism. While these goals are still far from being achieved, the identification of molecules such as ß-catenin and Sonic hedgehog (SHH) that are capable of inducing the formation of new hair follicles provides us with potential strategies for treating conditions in which follicles have been completely destroyed. SHH can induce anagen ***(Sato et al, 1999),*** a property that may be useful for treating a variety of conditions. In designing therapeutic approaches, however, it must be borne in mind that these molecules can also cause the formation of tumors such as Basal cell carcinoma (***Oro and Scott, 1998).*** It will therefore be important to ensure, by controlling the dose, or modifying the properties of these molecules, that one can induce follicle formation without producing harmful side-effects ***(Chan et al, 1999)***.

The development of methods for delivering genes to hair follicles is an area of active research that will clearly be critical

for achieving therapeutic goals ***(Alexeev et al, 2000; Domashenko et al, 2000).***

Although striking advances have been made recently in our understanding of hair follicle development, several areas remain mysterious. The next few years are likely to bring answers to some of these outstanding questions, and perhaps the beginnings of therapeutic applications for such recently acquired knowledge.

Aim of the work

The purpose of this essay is to summarize recent progress in our understanding of the molecular mechanisms regulating hair follicle formation and to discuss ways in which this information may eventually be utilized in our clinical practice.

Anatomy and Biology of Hair Follicle

The total number of hair follicles for an adult human is estimated at 5 million with 1 million on the head of which 100,000 alone cover the scalp. In humans, the only external regions of skin devoid of hair follicles are the palms and soles. The basic hair follicle structure remains essentially the same throughout the range of mammalian species with modifications for specialized functions. The hair follicle can be recognized as a separate entity within the skin with formation and maintenance based on interaction between dermal and epidermal components ***(Caserio, 1987***).Hair performs no vital function in humans, whose body could be perpetually depilated without any physiological disadvantages. At the same time the psychological functions are inestimable: scalp hair is major social and sexual display features of the human body (***Hashimoto, 1988)***.

The elaborate follicular innervation system is responsible for the properties of the hair follicle as a highly sensitive tactile organ, which registers even very delicate touch sensations brought about by hair shaft movements e.g. generated by insects, wind and stroking. In addition, the follicular neural plexus may also have important trophic and regulatory functions by the release of neurotransmitters, neuropeptides and neurotrophins ***(Peters et al., 2002)***.

Hairs grow out of tubular invaginations of the epidermis known as follicles, and a hair follicle and its associated sebaceous glands are referred to as a pilosebaceous unit. Hair follicles are situated at an oblique angle to the epidermal surface. This allows the layering of the hair shafts which results in the appearance of a protective shield over the underlying skin, and facilitates the use of hair shafts as a transport and spreading vehicle for sebum, apocrine sweat and skin debris ***(Poblet et al., 2002).*** A small bundle of smooth muscle fibers, the arrector pili muscle, extends from just beneath the epidermis and is attached to the side of the follicle at an angle. Arrector pili muscles are supplied by adrenergic nerves, and are responsible for the erection of hair during cold or emotional stress ('goose flesh'). The sebaceous gland is attached to the follicle just above the point of attachment of the muscle ***(Murphy, 1997).*** The hair follicle can be divided into 3 regions: the lower segment (bulb and suprabulb), the middle segment (isthmus), and the upper segment (infundibulum) (Figure1).The lower segment extends from the base of the follicle to the insertion of the arector pili muscle. The middle segment is a short section that extends from the insertion of the arector pili muscle to the entrance of the sebaceous gland duct. The upper segment extends from the entrance of the sebaceous gland duct to the follicular orifice.

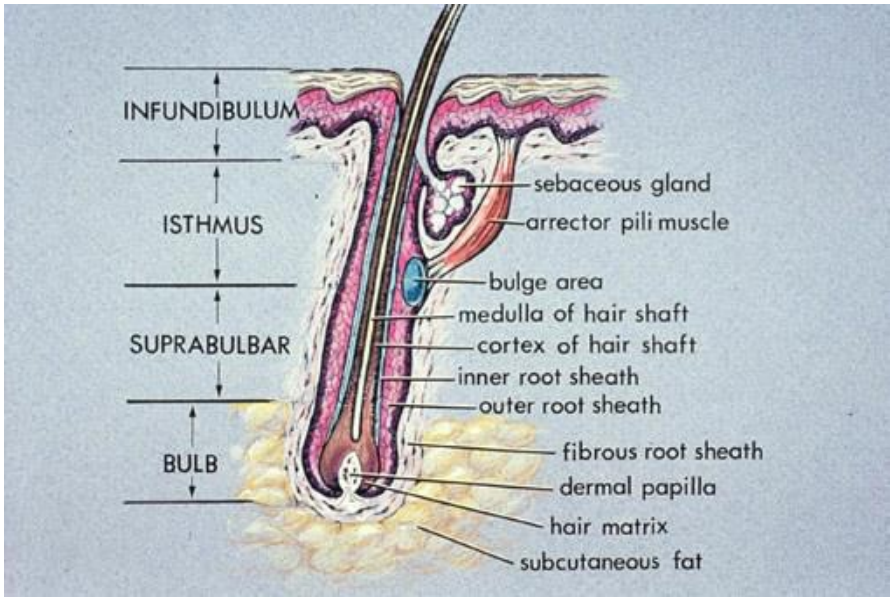

Figure 1: Structure of the hair follicle ***(Murphy, 1997).***

The hair bulb at the lower end of the follicle contains the hair matrix which is a zone of rapidly dividing cells responsible for the formation of the hair shaft. Hair pigment is produced by melanocytes in the hair bulb. Cells produced in the hair bulb become densely packed, elongated and arranged parallel to the long axis of the hair shaft. They gradually become keratinized as they ascend in the hair follicle. The average rate of growth of human scalp hair is 0.37mm per day. In women scalp hair grows faster and body hair grows more slowly than in men. The rate of growth of body hair is undoubtedly increased by androgens, since it can be reduced by treatment with antiandrogenic steroids (***Champion et al., 1992).***

The hair follicle as a whole is not only one of the most densely innervated peripheral organs in the mammalian body, but also displays a rich, basket-like vasculature. The vasculature arises from the dermal and subcutaneous vascular plexus, and is formed by arterioles, capillaries and venules with numerous shunts. This perfusion system ensheathes the entire follicle, weaving through its connective tissue sheath, and even inserts into the dermal papilla of terminal hair follicles. ***(Mecklenburg et al., 2000).*** All key regions of the hair follicle have abundant access to nutrients, oxygen and systemic bioregulatory molecules such as hormones ***(Yano et al., 2001).***

Embryology of the hair follicle:

In human foetuses, the first primordial hair follicles form at approximately 9 weeks gestation and are distributed mainly in the eyebrows, upper lip and chin. The bulk of the remaining follicles begins to develop approximately at the 4^{th} or 5^{th} month of gestation in a cephalo-caudal direction ***(Holbrook and Minami, 1991)***.

Follicular morphogenesis begins with an inductive event that involves the exchange of signals between epithelial and mesenchymal cells, and proceeds through stages of initiation, elongation and differentiation. The first indication that a hair follicle is about to form occurs in the "Pregerm" stage of development, where a focal crowding of nuclei in the epidermal basal layer is matched by a cluster of mesenchymal cells

beneath the basement membrane ***(Schmidt-Ullrich and Paus, 2005)***.

The crowding of basal keratinocytes causes a slight "bud" on the underside of the epidermis, which is termed placode (stage 1) then the follicle germ or primitive hair germ (stage 2). The next stage in follicular neogenesis is known as the follicle peg, which is the result of the elongation of follicle germ into a cord of epidermal cells that grows into the dermis roughly perpendicular to the skin surface (Figure 2) ***(Holbrook and Minami, 1991)***. Mesenchymal cells line the sides of the epidermal cord, and these cells eventually form the follicular sheath, while those mesenchymal cells concentrated at the tip eventuate into the follicular papilla. The tip of the epithelial cord is flattened and becomes the matrix portion of the bulb. As the follicles continue to elongate, the matrix forms the bulbous hair peg. The deepest portion of the bulbous hair peg forms an invagination surrounding the bulk of the underlying mesenchymal cells, which develop into the follicular papilla "Dermal Papilla". The matrix keratinocytes, located above the basement membrane overlying the follicular papilla, ultimately give rise to the hair shaft and inner root sheath. The outer root sheath, comprising the most peripheral epithelial cell layers of the follicle, is in continuity with the epidermis and is most likely not formed from the matrix cells**.** As the follicle begins to produce a hair the central cells of the rudimentary follicle degenerate forming the pathway through which the hair fibre will pass ***(Lavker et al., 2003)***.