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Derleme

EFFECTIVE GENES ON HAIR FOLLICLE GROWTH

Mehmet Cevat TEMIZKAN[1], Alev Gurol BAYRAKTAROGLU[2]

[1]Ankara University, Faculty of Veterinary Medicine, Department of Genetics, Ankara/Turkey
[2]Ankara University, Faculty of Veterinary Medicine, Department of Histology and Embryology, Ankara/Turkey

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ABSTRACT

Molecular studies have come to the fore within the scope of the development of animal breeding for animals whom used for hair fiber production. For this reason, genetic studies made or will be made on production and quality of hair in animals have become more of an issue. In animals like goat and sheep been rich in terms of textile products, hair structure is constitutively divided into two as primary and secondary. In studies made in these follicles, it is identified that the 10077 genes are expressed in the primary hair follicles and the 7772 genes are expressed in the secondary hair follicles. In this review, it will be summarized the anatomy and the process of development of the hair follicle generating the animal fibers, genes had an effect upon development of hair and the processes formed the hair follicle of these genes. In addition, it will be mentioned about structure of hair follicle and efficiency of genes; morphogenesis and cycle stages; anagen, catagen and telogen. The scope of this work includes examination of genes associated with quality from the formation of hair follicle to starting of first cycle and in the repetition of process continually.

Key Words: *Genes, gene expression, hair follicle, morphogenesis.*

İletişim / Correspondence
Ankara Üniversitesi, Veteriner Fakültesi, Genetik AD, Ankara, Turkey

0312 317 0315

cevat@hotmail.co.uk

KIL FOLİKÜLÜ GELİŞİMİ ÜZERİNE ETKİLİ GENLER

ÖZET

Kıl üretimi için kullanılan hayvan ırkların geliştirilmesi kapsamında moleküler çalışmalar ön plana çıkmaktadır. Bu nedenle hayvanlarda kıl üretimi ve kalitesi üzerine yapılan ve yapılacak olan genetik çalışmalar önem kazanmıştır. Keçi ve koyun gibi tekstil ürünleri açısından değerli hayvanlarda, kıl yapısı temel olarak primer ve sekonder olmak üzere ikiye ayrılmaktadır. Bu foliküllerle yapılan çalışmalarda primer foliküllerde 10077 genin, sekonder foliküllerde ise 7772 genin ifade edildiği tespit edilmiştir. Bu derlemede, hayvansal lifleri oluşturan kıl folikülünün anatomisi ve gelişim süreci, kıl gelişimine etki eden önemli genler ve bu genlerin, kıl folikülünü şekillendirme süreçleri özetlenecektir. Buna ek olarak kıl folikülünün yapısı, morfogenezi ve siklusun meydana geldiği anajen, katajen ve telojen aşamaları ve bu aşamalardaki genlerin etkinliğinden bahsedilecektir. Çalışmanın kapsamı; kıl folikülünün oluşumundan ilk siklusun başlamasına ve sürecin devamlı olarak tekrarında kalite ile ilişkilendirilmiş genlerin incelenmesini içermektedir.

Anahtar Kelimeler: *Genler, gen ifadesi, kıl folikülü, morfogenez.*

INTRODUCTION

Molecular methods have been begun to be preferred also in development and improvement of the animal fibers in recent years, as it happened in other characters that derived from animals and tried to increase their efficiency with variety of improvement methods for decades. As a consequence of this, improvement that will be made with molecular methods for development especially sheep wool, goat cashmere and mohair fibers also angora rabbit and alpaca fibers are used in textile sector will have given an opportunity of developing the characters more quickly and properly.

At the molecular level, a single hair follicle almost behaves like an mini-organ and is formed and developed by the activation of thousands of genes. In the light of informations revealed by the previous studies, together with the development of hair follicle to occur as a result of morphogenesis and cycle stages is known, also has been obtained a wide range of data about the molecular factors that generate these stages today.

Two kinds of follicles mainly has come into prominence. These are the primary and secondary follicles. While the upper rough hairs in goats is originated from primary hair follicles, the lower hairs like cashmere and mohair is based to secondary hair follicles. However, upper rough hairs are particularly more protective, the lower hairs serve in thermal insulation. Lower hairs are not affected too much by the physical conditions of environmental. Therefore, in sheeps and goats, cashmere and mohair which can be obtained only from lower hairs of goat have gained importance for the production of high quality products in textile sector (8). Development of primary hair follicles are faster than those of secondary hair follicles. However, high quality products used in textile and industry compose of secondary follicles (11, 46).

HAIR FOLLICLE

Hair Follicle Anatomy

The hair follicle is essentially divided into four regions. As it is seen in the figure below, bulb located undermost contains within

itself the matrix and the papillae that is responsible for formation and development of hair. Melanocytes given to hair its colour is also found on the matrix. Region of bulb is fed by vein and nerves (3). The area of stem located above the bulb contains of the bulge region that is between the bulb and the arrector pili muscle and that is source of stem cell for the hair within (23). Above this

At the horizontal section of hair follicle medulla region has been seen in the innermost layer of the hair and the same as from the inside out respectively the regions of cortex and cuticle. Cuticle is enwrapped respectively with inner root sheath, henle's layer, huxler's layer and outer root sheath and all of this structure unfold the hair shaft (3,12) (Figure 1).

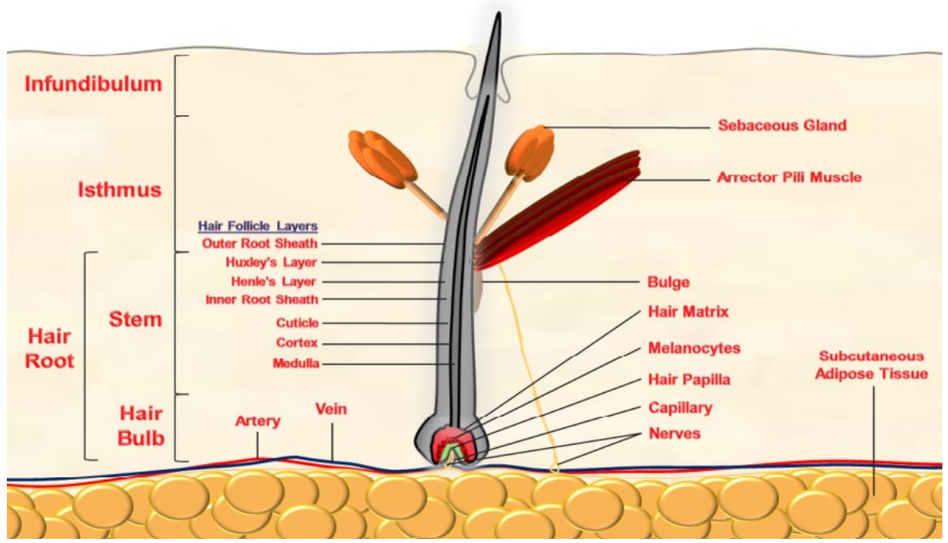

Figure 1: Hair Follicle Structure.

region where the arrector pili muscle and the sebaceous gland have been located, region of isthmus is found. In that region, arrector pili muscle is a muscle which is associated with the sebaceous gland, controlled by the sympathetic nervous system and responsible for the protection against predators, thermal insulation and for the hair follicle to arrive at surface.

Sebaceous glands along with providing for the hair to be soft, supple and waterproof by secreting sebum, serves as a lubricant for the hair to arrive the surface. Infundibulum region where the hair exit from surface is found in the upper region of the hair follicle (3,40) (Figure 1).

Morphogenesis and Cycle of Hair Follicle

Morphogenesis of hair follicles occur mainly in three stages. These stages are respectively induction stage where the first downgrowth called placode is formed, organogenesis stage where the hair germ and the hair peg take shape and cytodifferentiation stage where the structure of mature follicle come into existence (25) (Figure 2).

After the hair is formed once, it begins to a cycle consisting of anagen, catagen and telogen phases continuing during the life of organism as long as it is not exposed to any inhibitory factor. To exemplify; secondary follicles forming cashmere and mohair

fibers in goats undergo the active anagen phase between the months of June and November and grow average of 185 days. Catagen phase lasted average of 60 days follows this phase between the months of December and January. Then telogen phase lasted approximately 120 days occurs from February till the end of May and cycle lasts almost a year (40, 46).

Anagen phase is the first stage beginning during the regrowth and the morphogenesis that lower part of the follicle regenerated and that follow the telogen phase after the fall out but the hair shaft has any relation left with the organism so it will seperated automatically from that (1). In the course of transition from telogen phase to anagen, stem cells in the lower parts of telogen follicle and in the region near the dermal papillae is activated for the production of new hair shaft. These cells transform into young hair follicles changing rapidly. This mechanism occurs at the region called bulge in the hair structure. This region serves as a reservoir of stem cells for the formation of young hair follicles (2) (Figure 2).

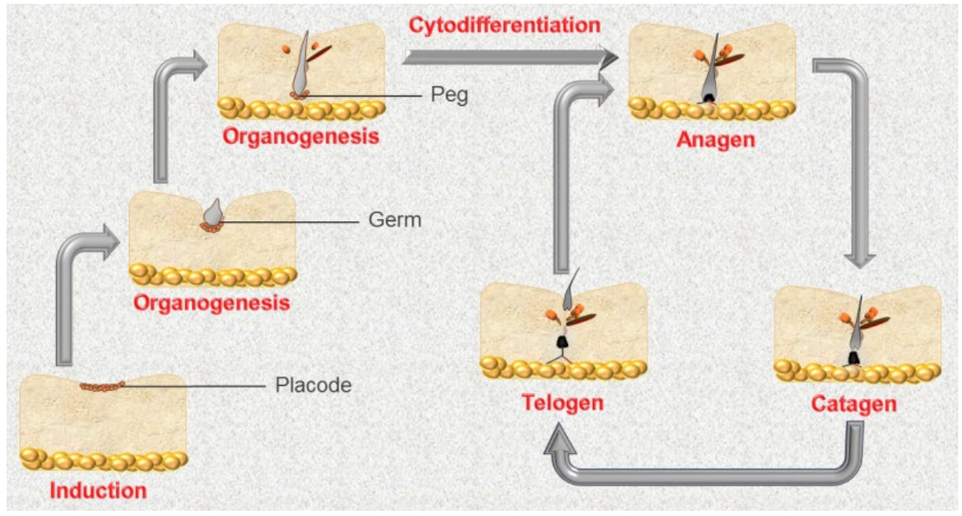

Figure 2: Hair Follicle Development.

formation of follicle. The anagen phase is completed, follicular development ends and the catagen phase begins. This phase involves the processes of the cell differentiation and completely under control apoptosis. Cell production and pigmentation cease to grow in the catagen phase, the papilla separates from the bulb (40). Hair follicle completes the cycle and is eliminated from the body in the resting phase of hair, telogen phase which is following the catagen. During the telogen phase there is no obligation for the hair to

Effective Genes on Hair Follicle Growth

There are thousands of genes which have an effect upon the development of the hair follicle. To illustrate, in a study made on goats it is identified that 10077 genes were expressed in goat primary follicles and 7772 genes were expressed in secondary follicles (Dong and et al., 2013). In this review, since it can not be mentioned the function of thousands of genes, it will be only touched on main genes making an effect to pathways.

Effective Genes on Morphogenesis

Mechanism of the first signal which provides the beginning have not been still understood in morphogenesis of the hair but it is thought that the effect of Wnt and β-catenin genes may have upon it (25; 39). It is dwelt on that a great number of dermal factors might be enable the beginning (39). With the signal given by the Wnt gene that is one of the most important genes synthesized from epidermis and enable the beginning, mesenchymal cells stimulate for the formation of placode and epithel cells stimulate for the thickening (34). Molecular markers such as Wnt10b, Ectodysplasin A (EDA), Ectodysplasin A Receptor (EDAR), Dickkopf Wnt Signaling Pathway Inhibitor – 4 (DKK4), Keratin 17 (KRT17) can be observed in the hair placode (39). Similarly, markers like Sex Determining Region Y–Box2 (SRY-box2: SOX2) and Syndecan 1 (SDC1) providing for dermal cells the specialization are also identified in the formation of placode under the epidermal region (10, 32).

Even if the primary signal is not known, Wnt synthesis is secondary signal triggering the formation of placode. Wnt5a synthesis is the first known signal, necessary for the beginning of Sonic Hedgehoc (SHH) gene synthesis from epithelial cells. Epidermal Wnt genes are required for the control of β-catenin signal and fibroblast proliferation. In the absence of dermal β-catenin signaling, activity of epidermal β-catenin and EDAR genes decreases. This makes impossible the fibroblast proliferation and the formation of hair follicle to occur without dermal β-catenin. For this reason, formation of fibroblasts and hair follicle could begin with the Wnt/β-catenin synthesis (34).

Epithelial Wnt/β-catenin synthesis regulates EDA/EDAR/Nuclear Factor Kappa-B (NF-κB) pathway. This pathway enables the development of follicle interacting with a large number of genes. For example, synthesis of EDA and EDAR suppresses the Bone Morphogenetic Protein (BMP) which gene have a function on placode formation inhibitor (26; 31; 47) (Figure3). And it is known that NF-κB is responsible for the formation and development of placode borders (47) (Table 1).

Condensation of dermal fibroblasts follows the occurence of placode formation. In condensation; synthesis of Fibroblast Growth Factor (FGF) gene synthesized from placodes and first stages of development of hair follicle is completed and this enables the dermal papillae to condensate (13). Besides it is thought that Fibroblast Growth Factor Receptor (FGFR1) gene may be one of initiator factors of the hair morphogenesis (6). In the formation of placode, genes of Keratinocyte Growth Factor (KGF also known as FGF7) and Epidermal Growth Factor (EGF) also have functions as inhibitory (28, 33) (Figure 3) (Table 1). Hair follicle begins to organogenesis when placode have enough amount.

Organogenesis is a stage characterized with simultaneous and massive increase of keratinocyte (34). In this stage, when dermal Noggin genes mediates the inhibition of BMP synthesis, it also helps the stages of development of hair follicle to be regulated through Lymphoid Enhancer Binding Factor 1 (LEF1) at the same time (4; 16). Regular working of EDA/EDAR/NF-κB pathway regulates the synthesis of SHH and Cyclin-D genes. Gene of SHH interaction with Cyclin-D genes, helps the epithelial proliferation and placode downgrowth (36). Synthesis of epithelial SHH and Noggin, initiates the maturing of dermal papillae. Expression of SHH is controlled by the synthesis of Wnt

and LEF1 genes. Synthesis of E-Cathedrin with LEF1 contributes also the expression of SHH gene to increase (41) (Figure 3). Gene of SHH is a gene controlling almost all the pathways and helping the hair germ to form in the stage of organogenesis. Expression of Noggin and genes related to it, enables the synthesis of Epithelial Platelet-Derived Growth Factor (PDGF). Gene of PDGF is important for emergence the mesenchymal-epithelial relations as well (39) (Table 1).

When it comes to the cytodifferentiation of hair follicle, GATA Binding Protein-3 (GATA3) transcription factors are responsible in the differentiation of inner root sheath the hair shaft from dermal papillae (35, 15, 7). Differentiation of outer root sheath occurs with the synthesizing of KRT6 and KRT16 proteins from Henle's layer found in the inner root sheath (35, 15). Dermal papillae activates the gene connecting to the promotor site of Wnt5a gene with Notch / Recombinant Signal Binding Protein for Immunoglobulin Kappa J Region. Expression of Wnt5a enables to be expressed of FOXN1 gene. And FOXN1 allows of the differentiation of keratinocyte in the hair follicle and makes available for melanocytes to pass from the keratinocyte to the hair cortex (34) (Figure 3) (Table 1).

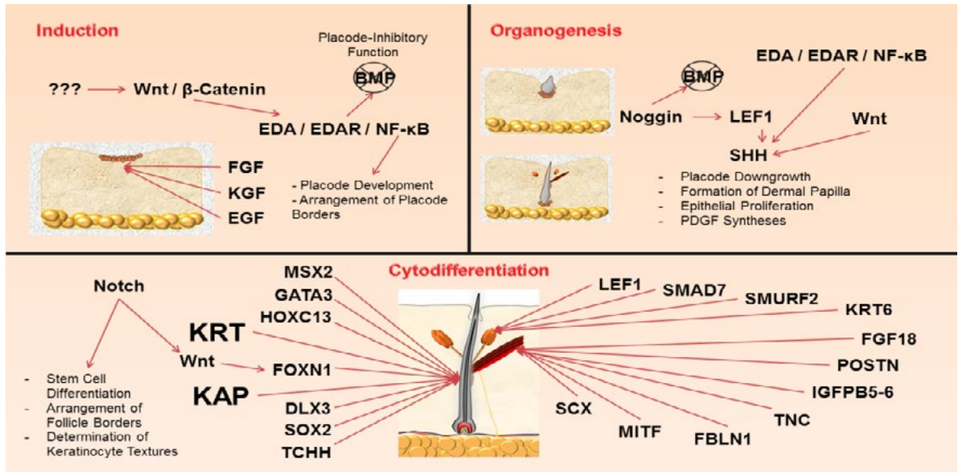

Figure 3: Effective Genes on Morphogenesis.

and likewise MSH Homeobox-2 (MSX2), Forkhead Box N-1 (FOXN1) and Homeobox C13 (HOXC13) transcription factors are responsible for the differentiation of hair shaft. In a study conducted before, it has ben observed that abnormal hair growth was happened in mice had GATA3 null mutation as a consequence of the nonformation of inner root sheath (18). While the genes of DLX3 and Trichohiyalin (TCHH) contribute the differentiation of hair shaft and inner root sheath, SOX2 gene controls the growth of

Notch family genes may have an effect upon the stage of cytodifferentiation in many different ways. These genes have functions for the differentiation of hair stem cells, determination of the hair borders and identification of properties of keratinocyte (5, 14) (Figure 3) (Table 1). Wnt gene works as a mediator for the selection of epidermal place where the hair will grow (44).

Arrector pili muscle arises from differentiation of stem cells found in the bulge region. Arrector pili muscle is formed

Table 1: Gene Functions on Morphogenesis

Gene Functions on Morphogenesis	
Induction	
Wnt5a	First known signal for induction
β-catenin	Formation of fibroblasts and hair follicle
EDA/EDAR	Suppresses placode formation inhibitors
NF-κB	Formation and development of placode borders
FGF	Dermal papillae condensation
KGF/EGF	Condensation inhibiton
Organogenesis	
Noggin	Inhibition of BMP synthesis and regulation of hair follicle development stages with LEF1 and synthesis PDGF
EDA/EDAR/NF-κB	Regulates the synthesis of SHH and Cyclin-D
SHH/Cyclin-D	Epithelial proliferation and placode downgrowth
SHH/Noggin	Initiates the maturing of dermal papillae
Wnt/LEF1	Controls SHH expression
E-Cathedrin/LEF1	Increase SHH expression
SHH	Controlling pathways and helping the hair germ to form
PDGF	Emergence the mesenchymal-epithelial relations
Cytodifferentiation	
GATA3	Differentiation of inner root sheath
MSX2, FOXN1, HOXC13	Differentiation of hair shaft
DLX3, TCHH	Differentiation of hair shaft and inner root sheath
SOX2	Controls the growth of the hair shaft
KRT6, KRT16	Differentiation of outer root sheath
Wnt5a, FOXN1	Differentiation of keratinocyte
Notch	Differentiation of hair stem cells and determination of the hair borders and identification of properties of keratinocyte
SCX, MITF, IGFBP5-6, FBLN1, POSTN, TNC, FGF18	Differentiation of arrector pili muscle
Wnt/β-catenin, SHH, LEF1, SMAD7, SMURF2, KRT6	Differentiation of sebaceous glands
Many genes are under control of pleiotropic or epistatic effect. These information given above are broad and does not contain entire functions of the genes.	

as a result of the expression of tendon genes such as Skleraxis (SCX), Microphthalmia-Associated Transcription Factor (MITF), Insulin-Like Frowth Factor Binding Proteins (IGFBP5-6), Fibulin-1 (FBLN1), Periostin (POSTN), Tenasin-C (TNC), FGF18 (43). Development of sebaceous glands takes place after Wnt/β-catenin and the signal of SHH occurs. Growth of sebocyte is also formed with the differentiation of stem cells found in the bulge region. Growth of sebaceous glands and generation of secrate occurs in the sebocytes with the effect of LEF1, SMAD7, SMURF2, KRT6 genes (27) (Figure 3) (Table 1).

Effective and Quality Related Genes on Cycle

Anagen phase is an active phase that synthesis products of numerous genes are involved in an interaction with each other between the dermal papillae and the matrix. But if follicle is examined in terms of the hair quality, genes of KRT and KAP

which are the main structural proteins of hair fibers are distinguished. Proteins of KRT and KAP are the primary proteins evaluated for the determination of hair quality (Table 2). Keratin involves two kinds of multiple gene families as type 1 and type 2; and all of them play a part in the skeletal structure of hair. KAP contains by far a wide-ranging multiple gene family and basically can be classified as High-Sulfur, Ultra-High Sulfur and High Glycine-Tyrosine KAP (9). Particularly in cashmere goats, keratin level of wool is affected by High Glycine-Tyrosine KAP. KAPs consisting of High Glycine-Tyrosine KAP are synthesized by gene families of KAP 6n, KAP 7, KAP 8 (17). Thus, it is made a research on frequently KAP 6, KAP 7 ve KAP 8 in the studies conducted about the KAP genes. For example, in a study made on Merinos sheeps, it has been found the relation of KAP 6 and KAP 8 genes with the hair length (30). In a research conducted on cashmere quality of goats, it has been discovered that genes of KAP 8.1 and KAP 8.2 are directly associated with cashmere quality (48). In other study, characterization and expression levels of KAP 7.1 and KAP 8.2 genes in cashmere goats have been examined using technique of in situ hybridization; high incidence of KAP 7.1 synthesis has been detected in the cortical layer for both primary and secondary follicles (17). In a another research, it has been determined that 10 of 30 different KAP genes in goats are synthesized in the secondary follicles more higher than primary follicles. All of these 10 KAP genes synthesized in a different way have the feature of ultra high sulfur (9). Another research on sheep, goat, rabbit and alpaca shows that rabbit fibers contains more KRT and KAP proteins comparing with other three species (42).

Keratin structure of hair is in alpha-keratin form and called also as the hair keratin. Alpha-keratin is frequently used in determination of the quality in cashmere and wool because of the fact that it is found in structures of primary and secondary follicles. To illustrate; it has been seen that genes as of KRT33A in the first place (medulla, cortex and cuticle have been identified in the interior and exterior stem sheath), KRT31, KRT32, KRT34, KRT35, KRT36, KRT37, KRT38, KRT39, KRT40 in goat primary and secondary follicles may be associated with the hair quality (38). Besides it has been confirmed that KRT14 and KRT19 from type 1 keratins, KRT5 and KRT19 from type 2 keratins again in goats showed increase between the months of August and December (20). In still another work, it has been revealed that genes of KRT5, KRT14, KRT17, KRT25, KRT27, KAP13.1, KAP9.2 also have an effect on the development of follicle showing different gene expressions in different periods of hair growth (21).

It is known that genes of Homeobox (HOX) also have influence over the hair follicle development. HOXC8 and HOXC9 genes expressed by matrix and dermal papilae depending on the gene serves in the implanting of the hair follicle and the hair shaft (40). In a research conducted, it has been observed that genes of Hoxc13/β-catenin affected the activity of follicle. This research have revealed that the genes of excessive HOXC13 and MSX2, Delta, BMP2, Neurotrophic Tyrosine Kinase, Receptor, Type 3 (Ntrk3) decreased the follicle development and the genes of PDGF, FGF5, Wnt10b, Frizzled-related Protein (FRZB), TGF-β, Nanog Homeobox (Nanog) increased the hair development in goats (46) (Table 2).

Hair follicles in the anagen phase contains apoptotic cells within itself. These cells is found particularly in the region of medulla, inner root sheath and bulb. When the anagen phase is completed, the catagen phase begins with the transduction of first signal (40). Although the first signal has not been known for certain yet, a recent study made in mice has showed that the gene of Gasdermin-A3 (Gsdma3) might have been the initiator gene (19). In another study conducted on the goats, it has been thought that the gene of FGF21 may be a factor beginning the catagen phase (9). The most well known first signal is the halt of IGF-I and Hepatocyte Growth Factor (HGF) expressions (40). One of the most important inductives from the catagen phase is FGF5 gene (37). Genes preventing the apoptotic signals are B-Cell Lymphoma (BCL) and Inhibitor of Apoptosis (IAP). Synthesis of Tumor Necrosis Factor β-1 (TNFβ1) gene increase with inhibition of BCL and related genes in the catagen phase (40) (Table 2).

When it comes to passing telogen phase from the catagen, reproduction of cells and their biochemical activity shows a decrease compared to the other stages. Old hair shaft remained from previous cycle is discarded from the follicle. Eventhough it is known as a resting stage for the hair follicle, fundamental changes are occured in the activity of a large number of genes also in the telogen phase (37).

Towards the end of the telogen phase, Nuclear Factor 1C (NF1C) is activated and accommodates the expressions of SHH, Wnt5a, LEF1 genes. NF1C increases the keratinocyte proliferation enabling the activation of TGF-β1 gene at the same time (34). As a consequence of the inactivation of BMP2 and BMP4 genes, the anagen phase begins again with the activation of Wnt/β-catenin signal (37). During the transition from the telogen to the anagen phase, TGF-β2 gene functions in the regeneration of hair follicle

Table 2: Effective Genes on Cycle

Effective Genes on Cycle	
Anagen	
KRT, KAP	Plays role in skeletal structure of hair
HOXC8, HOXC9	Implanting of the hair follicle and the hair shaft
HOXC13 and MSX2, Delta, BMP2, Ntrk	Decrease the follicle development
PDGF, FGF5, Wnt10b, FRZB, TGF-β, Nanog	Increased the follicle development
Catagen	
IGF-I, HGF	Catagen phase signal
FGF5	Inductives from the catagen phase
BCL, IAP, TNFβ1	Role on apoptosis
Telogen	
NF1C	Activates SHH, Wnt5a, LEF1, TGF-β1
TGF-β1	Increases the keratinocyte proliferation
BMP2, BMP4	Role on apoptosis
Wnt/β-catenin	Lead to begining of anagen
Transition from telogen to anagen	
SHH, Wnt/β-catenin, TGF-β2/SMAD2/SMAD3, Tmeff1, BMP, Notch, LEF1, STAT3, Noggin, FRZB, Wif1, FGF, Inhba, Gli, Cyclin D	
Many genes are under control of pleiotropic or epistatic effect. These information given above are broad and does not contain entire functions of the genes.	

and the activation of SMAD2 and SMAD3 pathway found in the hair follicle stem cells. TGF-β2/SMAD2/SMAD3 pathway affects on genes of EGF and Transmembrane Protein with EGF-Like and Two Follistatin-Like Domains-1 (Tmeff1) (Table 2). These genes makes an effect for the stem cells to pass from the telogen to the anagen phase inhibiting BMP gene and contribute the production of new hair (29).

Transition from the telogen to the anagen phase occurs by way of signal ways such as SHH, Wnt/β-catenin, BMP, Notch, LEF1 and Signal Transducer and Activator of Transcription 3 (STAT3) and the genes of Noggin, FRZB, Wnt Inhibitory Factor-1 (Wif1), FGF, Inhibin β-A (Inhba), Gli, Cyclin D (24; 39; 49) (Table 2). However, β-catenin signal may be enough by itself for giving a start to the anagen phase (22).

CONCLUSIONS

In this review, it has been based on the studies made on a lot of animal species. Despite the fact that the basic mechanism of hair follicle development is similar in the interspecies, it should not be expected that as a complex miniorgan and emerged with working of thousands of genes, the hair follicle would develop in the same way in all animals. Even in the primary and the secondary hair follicles in goats, hundreds of genes is expressed in different levels. After all, this review is prepared with the purpose of revealing outlines of the hair follicle development.

There are innumerable questions that had not yet revealed including the beginning in the mechanism of hair follicle. Studies made at the molecular level bring along the new findings oriented the morphogenesis and cycle of hair follicle and make the humankind to approach on the solution of mechanism one more step. Consequently; when the hair follicles occur with morphogenesis and carry out regular cycles during the life of organism after occured, signal molecules and pathways emerged in this process should be clarified in detail. Elucidating of genes and pathways developed with the effect of these genes is also crucial for the growth of livestock and textile industry.

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