EFFECTIVE GENES ON HAIR FOLLICLE GROWTH

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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.
At the molecular level, a single hair follicle almost behaves like a 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 hair follicles, the lower hairs like cashmere and mohair is based to secondary hair follicles. While the upper rough hairs are 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 faster than those of secondary hair follicles.

At the horizontal section of hair follicle 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 separated 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.**

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 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 Hedgehog (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-xB) 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) (Figure 3). And it is known that NF-xB is responsible for the formation and development of placode borders (47) (Table 1).

Condensation of dermal fibroblasts follows the occurrence 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) 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-xB 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...
Effective Genes on Morphogenesis

**Table 1: Gene Functions on Morphogenesis**

<table>
<thead>
<tr>
<th>Induction</th>
<th>Gene Functions on Morphogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wnt5a</td>
<td>First known signal for induction</td>
</tr>
<tr>
<td>β-catenin</td>
<td>Formation of fibroblasts and hair follicle</td>
</tr>
<tr>
<td>EDA/EDAR</td>
<td>Suppresses placode formation inhibitors</td>
</tr>
<tr>
<td>NF-kB</td>
<td>Formation and development of placode borders</td>
</tr>
<tr>
<td>FGF</td>
<td>Dermal papillae condensation</td>
</tr>
<tr>
<td>KGF/FGF</td>
<td>Condensation inhibition</td>
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</tbody>
</table>

**Organogenesis**
- Noggin: Inhibition of BMP synthesis and regulation of hair follicle development stages with LEF1 and synthesis PDGF
- EDA/EDAR/NF-kB: 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-Cathelin/LEF1: Increase SHH expression

**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.

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 as a result of the expression of tendon genes such as Skleraxis (SCX), Microphthalmia-Associated Transcription Factor (MITF), Insulin-Like Growth Factor Binding Proteins (IGFBP5-6), Fibulin-1 (FBLN1), Peristin (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 secrete 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...
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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 Merino 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 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 papillae 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 Hoxc13β-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 decreased the follicle development (21).

Hair follicles in the anagen phase contains apoptotic cells within itself. These cells are 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 Gadermin-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 (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 off from the follicle. Evenhough it is known as a resting stage for the hair follicle, fundamental changes are occurred 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 Wntβ-catenin signal (37). During the transition from the telogen to the anagen phase, TGF-β2 gene functions in the regeneration of hair follicle

<table>
<thead>
<tr>
<th>Effective Genes on Cycle</th>
<th>Telogen</th>
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</thead>
<tbody>
<tr>
<td>KRT, KAP</td>
<td>Plays role in skeletal structure of hair</td>
</tr>
<tr>
<td>HOXC8, HOXC9</td>
<td>Implanting of the hair follicle and the hair shaft</td>
</tr>
<tr>
<td>HOXC13 and MSX2, Delta, BMP2, Ntrk</td>
<td>Increase in hair follicle development</td>
</tr>
<tr>
<td>PDGF, FGF5, Wnt10b, FRZB, TGF-β, Nanog</td>
<td>Decrease in hair follicle development</td>
</tr>
<tr>
<td>Catagen</td>
<td></td>
</tr>
<tr>
<td>IGF-I, HGF</td>
<td>Catagen phase signal</td>
</tr>
<tr>
<td>FGF5</td>
<td>Inductives from the catagen phase</td>
</tr>
<tr>
<td>BCL, IAP, TNFβ1</td>
<td>Role on apoptosis</td>
</tr>
<tr>
<td>Telogen</td>
<td></td>
</tr>
<tr>
<td>NF1C</td>
<td>Activates SHH, Wnt5a, Lef1, TGF-β</td>
</tr>
<tr>
<td>TGF-β1</td>
<td>Increases the keratinocyte proliferation</td>
</tr>
<tr>
<td>BMP2, BMP4</td>
<td>Role on apoptosis</td>
</tr>
<tr>
<td>Wntβ-catenin</td>
<td>Lead to beginning of anagen</td>
</tr>
<tr>
<td>Transition from telogen to anagen</td>
<td></td>
</tr>
<tr>
<td>SHH, Wntβ-catenin, TGF-β2,SMAD2/3, Smad3, Tmeff1, BMP, Notch, Lef1, Stat3, Noggin, Frzβ2, Wnt5, Fgf, Ihh, Gli, CycD</td>
<td>Inhibit of telogen</td>
</tr>
</tbody>
</table>

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Table 2: Effective Genes on Cycle
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 signaling may be enough by itself for giving a start to the anagen phase (22).

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REFERENCES
new hair follicles but continuous activation is required to maintain hair follicle tumours. Development. 2004; 131: 1787-1799.


