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REVIEW ARTICLE

Molecular Mechanisms Affecting Development of Animal Fibers and Some Studies on Goats

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Abstract

Natural fibers are of two types as vegetable and animal origin. Animal fibers have contributed to the development of the economic structures of the countries and the continuation of their traditions since ancient times and continue to do so. Various studies have shown that the properties of the fiber produced by the hair follicle are of great importance in determining fiber quality and quantity. Hair follicles have been developed in an environment where various molecular signals are effective. In this context, the investigation of molecular mechanisms affecting hair follicle development has come into prominence and it is seen that it has become the focus of studies. In this review, it has been tried to explain the importance of animal fibers and the molecular mechanisms affecting hair follicle morphogenesis and cycle by providing some examples from the studies on two goat breeds, Angora goat and cashmere goat, which are valuable in terms of animal fiber, leading to provide a preliminary information to the studies which has become the focus of today.

Introduction

Natural fibers are two types: plant and animal. Plant fibers produced at industrial level are cotton, kapok, flax, hemp, jute, sisal, manila hemp, coco fiber, while animal fibers are fleece, silk, mohair, cashmere, Angora rabbit wool, goat top coarse fibers and fibers obtained from Asian and South American camels (Dellal *et al*., 2010).

As environmental pollution has reached serious levels, the need, demand and interest in biodegradable, environmentally friendly products and sustainable production has increased. This situation is also reflected in the interest in natural fibers and therefore animal fibers from environmentally sensitive products in the textile sector (Selli *et al*., 2018). Animal fibers constitute the raw material of both traditional and industrial fiber processing systems (Gul *et al*., 2023). With this feature, it has contributed to the development of the economies and traditions of countries since time immemorial and continues to do so (Dellal, 2021).

Animal fibers are generated by hair follicles in the skin. They have specific growth, development and self-renewal mechanisms (Zhang *et al*., 2009). Hair follicles are considered as mini-organ formed as a result of neuroectodermal-mesodermal interaction (Schmidt-Ullrich *et al*., 2005).

The hair follicle is first formed during the embryonic period, and its growth is completed in this period as well (Dellal, 2021). This morphogenesis that occurs during the embryonic period includes three stages: induction, organogenesis and cytodifferentiation (Houschyar *et al*., 2020).

After birth, hair follicles are developed in a cycle known as hair follicle cycle. This cycle includes anagen (growth), catagen (regression) and telogen (relative stagnation) phases. Each phase of hair follicle cycle has its own unique mechanism of gene activation and silencing. The transition from one phase to another is controlled by transcription factors and enzymes recognized by the local signaling environment, cytokines, hormones, neurotransmitters and key mediator molecules (Yuan *et al*., 2013). Hair follicle development and hair growth are mediated by ectodermal-mesodermal interactions before and after birth, respectively (Sennett and Rendl, 2012).

To the best of our knowledge, most of signaling molecules that regulate hair follicle morphogenesis belong to Wnt pathway (Li *et al*., 2004), fibroblast growth factor (FGF) family, tumor necrosis factor (TNF) family (Millar, 2002), bone morphogenetic protein (BMP) family (Thomadakis *et al*., 1999), Sonic hedgehog (Shh) transduction pathway (McMahon *et al*., 2003), transforming growth factor (TGF) family (Ullrich and Paus, 2005) and Notch transduction pathway (Crowe *et al*., 1998). Some of them show activator and some inhibitory effects (Shang *et al*., 2021). However, the exact nature, timing, and intersections of these signaling pathways remain unclear (Sennett and Rendl, 2012).

miRNAs and lncRNAs are other molecules that regulate hair follicle development and regeneration in mammals. Liu et al. (2012) identified 316 conserved miRNAs and 22 novel miRNAs in Mongolian cashmere goats and predicted that miR-203 may play an important role in the development of skin and hair follicles. miR-203 was confirmed to regulate the development of cashmere goat hair follicle by targeting NAE1 and DDOST gene (Ma *et al*., 2021).

Expression analysis showed that lncRNA-000133 was more highly expressed in the anagen phases than in the telogen phase in cashmere goats. This suggests that this long non-coding RNA (lncRNA-000133) may be involved in formation and growth of cashmere fiber and restructuring of secondary hair follicles. Overexpression of lncRNA-000133 led to relatively significant increase in the expression of ALP, ET-1, LEF1 and SCF genes in dermal papilla cells, suggesting that lncRNA-000133 contributes to inductive property of dermal papilla cells (Zheng *et al*., 2020).

Most studies indicate that hair follicle characteristics and/or genetic regulatory mechanisms directly affect fiber production and quality (Nixon *et al*., 1991; Millar, 2002; Fu *et al*., 2020; Han et al., 2018; Su *et al.,* 2018; Wang *et al*., 2021; Wang *et al*., 2017; Qiao *et al*., 2016; Shang *et al*., 2021; Wang *et al*., 2015; Wu *et al*., 2022; Pazzaglia *et al*., 2019; etc.). More knowledge and better understanding of development and biological properties of the fiber formed by the hair follicle can provide important approaches to obtain the fiber with the desired properties (Gao *et al*., 2016; Arzik *et al*., 2023a). Fiber fineness and quantity are the most important factors determining its economic value (Arzik *et al*, 2023b). Therefore, knowing the regulatory effect of genes, signaling pathways and all mechanisms affecting hair follicle development on animal fiber is great importance in obtaining finer fiber.

Angora goat, which is an important genetic resource of our country, and cashmere goat are two goat breeds that are mainly bred for their fiber. Although there are mostly studies on cashmere goat, studies on these two goat breeds to determine the molecular mechanisms affecting hair follicle development are very valuable and it is seen that more studies are needed to obtain finer fiber.

In this review, the molecular mechanisms that provide hair follicle development and examples of studies on cashmere and Angora goats are given and it is aimed to provide preliminary information for future studies on this subject.

Molecular Mechanism of Hair Follicle Morphogenesis

Hair follicle morphogenesis consists of induction, organogenesis and cytodifferentiation and is mediated by signaling molecules.

Induction: The first structure formed as a result of thickening of the epidermis is called placode. The first dermal signal that enables the formation of this structure comes from the mesenchyme (Rishikaysh *et al*., 2014). In the absence of β-catenin, it has been determined that the placode structure does not form (Huelsken *et al*., 2001). However, the nature of the signal that initiates placode formation has not been fully elucidated (Wang *et al*., 2012). Wntless (Wls) protein is involved in Wnt secretion (Huang *et al*., 2012). Wnt signaling is another signal that is effective in placode formation.

Another important signal during the induction phase is Eda/Edar/Nuclear Factor Kappa-B (NF-κB) (Durmowicz *et al*., 2002; Laurikkala *et al*., 2002). Follistatin (FS), fibroblast growth factors (FGFs), MSX1 and MSX2, Noggin and TGF-β2 have a positive effect while BMPs have negative effect on placode formation (Wang *et al*., 2012). In addition, keratinocyte growth factor (KGF) and epidermal growth factor (EGF) block hair follicle formation (Richardson *et al*., 2009). Noggin signaling is important for the maintenance of hair follicle formation. Noggin knock-out mice were found to have a significant delay in hair follicle induction. Noggin eliminates the inhibitory effect of BMP-4 (Botchkarev *et al*., 1999).

Organogenesis: After the formation of the placode structure, some of the cells in the mesenchyme cluster to form the ‘dermal condensate’ under the influence of the epithelial signal from the placodes. Wnt signaling acts as an epidermal signal in the formation of the dermal condensate (Millar, 2002). As a result of the so-called ‘second dermal signal’ from the dermal condensate, placode proliferate, invade the dermis and surround the dermal condensate, forming a structure called the dermal papilla (Hardy, 1992). The main signal involved in dermal papilla formation and maturation is the Shh signal (Chiang *et al*., 1999; St-Jacques *et al*., 1998). The proliferation of placodes and the formation of dermal condensate structure indicate that the organogenesis phase has started. EDA (Ectodysplasin-A)/ EDAR/ NF-ΚB is also important signaling pathway in the progression of organogenesis. EDA/ EDAR/ NF-ΚB signaling is involved in the activation of epithelial Shh (Sonic hedgehog) and cyclin D1 expression (Schmidth-Ullrich et al., 2006). The EDA/EDAR signaling pathway can be summarized as EDA→ EDAR→ EDARADD→ NF-κB→ Shh→ Cyclin D1. The expression of Cyclin D1 is initiated by Wnt10b or Shh signaling (Andl *et al*., 2002; Schmidth-Ullrich and Paus, 2005; Laurikkala *et al*., 2002). TGF-β2 signaling provides the basis for transient induction of Snail, a transcription factor, and activation of the Ras-mitogen-activated protein kinase (MAPK) pathway in the hair bud (Jamora *et al*., 2005).

Cytodifferentiation: With cytodifferentiation, the entire hair follicle is formed. It has been determined that many signaling pathways are effective in the differentiation phase. Wnt/β-catenin and Lef1 signaling are among the signals that are important in hair structure differentiation (Botchkarev and Paus, 2003). Notch signaling pathway also plays a role specific differentiation of the hair structure. It has been determined that overexpression of Notch-1 causes the hair medulla to be abnormal and the fiber cover to be wavy and shiny. Notch and Jagged-1/2, the ligand of Notch-1, are effective in the differentiation of the inner root sheath and hair shaft (Lin *et al*., 2000; Kopan and Weintraub, 1993; Powell *et al*., 1998; Favier *et al*., 2000). Wnt5a mediates Notch signaling by facilitating the expression of the FoxN1 gene. While Wnt signaling has a positive effect on the Notch signaling pathway, recent data suggest that *Notch* has an antagonist effect on Wnt (Hayward et al., 2005; Proweller *et al*., 2006). FoxN1 regulates both the differentiation of hair follicle keratinocytes (Mecklenburg *et al*., 2001) and signals pigment transport from melanocytes to keratinocytes in the hair cortex (Weiner *et al*., 2007). Notch can contribute to hair follicle development in three ways: lateral inhibition, the formation of boundaries of the structures that make up the hair follicle, and the decision of which cell line to become. Notch mediates differentiation by suppressing p63 expression (Nguyen *et al*., 2006). Notch, Wnt and vitamin A are part of interconnected pathways involved in the selection of epidermal cell line (Watt *et al*., 2006).

Molecular Mechanisms Affecting the Hair Follicle Cycle

Our knowledge of the molecular mechanisms involved in the hair follicle cycle is mostly based on studies with mice. The signals that initiate the anagen phase are Wnt/β-catenin, BMP antagonists and sonic hedgehog (Cotsarelis and Botchkarev, 2008; Stenn and Paus, 2001; Paus and Foitzik, 2004; Hebert *et al*., 1994). The effect of hepatic growth factor (HGF), insulin-like growth factor-1(IGF-1) and vascular endotelial growth factor (VEGF) are reported to be important in maintaining the anagen phase (Paus and Foitzik, 2004).

The transition from anagen to catagen Keratin 17 and TNF-α signaling and is controlled by vitamin D receptor (VDR), retinoic acid receptor and Hairless (Hr) transcriptional receptor (Chuma *et al*., 2012; Wu *et al*., 2014). Neurotrophins such as NT3, NF4 and BDNF, interleukin-1β, TGF-β1 are reported to induce catagen (Foitzik *et al*., 2005). FGF-5 is thought to be critical in this transition (Oh *et al*., 2016). Because it has been determined that in case of any defect in FGF-5, the transition from anagen to catagen is delayed. This results in the formation of an excessively long hair structure called the ‘angora’ phenotype (Rishikaysh *et al*., 2014; Hébert *et al*., 1994). Hairless, regulates transcription by interacting with VDR. In the absence of these regulators, dermal cysts are formed (Teichert *et al*., 2010).

Although the telogen is characterized as the resting phase, it is the phase in which some major changes occur (Lin *et al*., 2004). Telogen consists of two sub-phases: refractor phase and competent phase. In the refractor phase, BMP2/4 is upregulated, and hair follicles show resistance to growth stimuli. In the competent phase, there is susceptible to signals that will initiate anagen and efficiency of BMP signaling decreases (Plikus *et al*., 2008). It has also been found that the expression of estrogen receptor is significantly upregulated during telogen (Ohnemus *et al*., 2005).

Some Studies with Goats

Diao *et al*. (2023) suggested that secondary hair follicle development in kids determines cashmere quality in adults and conducted an experimental study to support this idea. They suggested that secondary hair follicle development is completed at five-six months of age and FGF2, FGF21 and BMP7 may play a regulatory role in this development. They stated that hair follicle characteristics can be used as a parameter for breeding selection of cashmere goats at the age of six months of age.

In the study by Cinar-Kul *et al*. (2022), skin biopsy materials were taken from Angora goats in anagen and telogen phases. Expression levels of BMP-2, FGF-5, HOXC13, KAP9.2 and TGFBR2 genes were analyzed. It was determined that TGFBR2, FGF-5 and BMP-2 genes were significantly upregulated in the anagen phase, while the expression of KAP9.2 gene did not differ between the two phases. HOXC13 gene showed a high level of expression in the anagen phase, while expression of this gene was not detected in the telogen phase. The researchers stated that HOXC13 may be one of the factors underlying the shinier and silky and non-medular hair structure of mohair.

Wu *et al*. (2022) took skin samples from Jiangnan cashmere goats at three phases of the hair follicle cycle. Genes affecting hair follicle cycle and development and the interactions of mRNAs and lncRNAs associated with these genes were investigated. They identified 228 differentially expressed mRNAs and 256 lncRNAs. Several key genes including CHST1, CDKN1A, DEFB103A, SH3BP4, GAREM1, GSK-3β, KRTAP9-2, KRT2, KRT39, YAP1, S100A7A, FA2H, LOC102190037, LOC102179090, LOC102173866, FAM167A, FAT4 and EGFL6 have been shown to have important roles in hair follicle development and cycling. These genes are associated with Wnt/β-catenin, ERK/MAPK, NFκB/p38MAPK, TGFβ, Sonic hedgehog, mTORC1, caspase-1 and interleukin (IL)-1a signaling pathways.

In the study by Liu *et al*. (2022), melatonin was implanted into cashmere goats, and then skin samples were taken, and transcriptome sequencing and weighted gene co-expression analysis (WGCNA) were performed. One of the 14 co-expression modules identified by WGCNA was found to be associated with cashmere development after melatonin implantation. KEGG analysis revealed that the initial onset of melatonin-induced cashmere development was mainly related to the signaling pathway regulating stem cell proliferation and the Hippo, TGF-β and MAPK signaling pathways. Analysis of differentially expressed genes identified six hub genes including BMPR2, BMPR1A, PDGFRA, PPP2R1A, SMAD1 and WNT5A.

Zhao *et al*. (2022) investigated the underlying difference between fine ad coarse fiber in Tibetan cashmere goats by using proteomic and transcriptomic data. A proteomics approach identified 1.980 proteins. After comparative analysis of cashmere with coarse fiber and extremely fine fiber, 29 differentially expressed proteins (DEPs) were identified, such as APOH, AEBP1, CP, CPB2, CTSZ, GANAB, GLB1, GPR142, VTN, IMPA1, and HMCN1. Functional enrichment analysis of these DEPs showed that they are involved in cell redox homeostasis, oxidation-reduction process, metabolic, Wnt, PI3K-Akt, MAPK and signaling pathways. Transcription factor enrichment analysis revealed that the proteins mainly belonged to NF-κB family, HMG (high mobility group) family and CSD family. Western blotting confirmed the protein abundance of four DEPs (AEBP1, GC, GPR142 and VTN) and suggested that these are the most potential candidate genes for cashmere traits in Tibetan cashmere goats.

Işık *et al*. (2021) analyzed the genetic variation KAP1.1, KAP1.3 and K33 genes by DNA sequencing method by taking samples from Angora, Norduz, Honamlı, Kilis and Hair goat breeds of our country. A total of 59 nucleotide variations and indels (insertions/deletions) in KAP1.1 gene, 15 nucleotide variations and indels in KAP1.3 gene, 16 nucleotide variations and indels in K33 gene were determined in the analyzed samples. Keratin-mediated filament proteins (KIF or KRT) and keratin-associated (KAP) proteins play an important role in determining the structural and mechanical properties of hair and mohair fibers. Considering this situation, it was stated that there is a need to determine the relationship between the variation detected in KAP1.1, KAP1.3 and KRT1.2 genes and mohair yield and quality in this study.

In a study by Li *et al*. (2021), the expression profiles of long non-coding RNAs (IncRNAs) were analyzed using Zhongwei goats aged 45 and 108 embryonic days. In total, 46.013 mRNAs and 13.549 lncRNAs were identified, of which 352 mRNAs and 60 lncRNAs were differentially expressed. After functional enrichment analysis, it was determined that the genes targeted by lncRNAs were mainly involved in PI3K-Akt, arachidonic acid metabolism, cAMP, Wnt and MAPK signaling pathways. When qRT-PCR and WGCNA results were evaluated together, it was stated that LOC102172172600 and LOC102191729 may affect hair follicle development and wool curvature. KEGG pathway analysis showed significant enrichment of pathways including MAPK, TNF and PI3K-Akt, which play important roles in the regulation of hair follicle development.

Wang *et al*. (2021) attempted to determine the mechanism of periodic development of the hair follicle. With WGCNA, 10 co-expression modules were obtained, including 7.689 protein-coding genes. Of these, six were considered to be significantly associated with hair follicle development. In addition, functional enrichment analysis was performed for each module, and it was shown that it is closely related to ECM-receptor interaction, focal adhesion, estrogen signaling pathway, PI3K-Akt signaling pathway, etc. When this information was combined with the analysis of differentially expressed genes, 12 hub genes (AQP3, ANTKMT, COL1A1, C1QTNF6, COL1A2, DERL2, FA2H, KRTAP3-1, KRTAP11-1, NDUFS5, MRPL14, and XAB2) were selected as candidate markers. It has been stated by the relevant researchers that these genes can be used in the improvement of cashmere fiber production.

In the study by Ahlawat *et al*. (2020), transcriptome pattern of skin samples from Changthangi goats with fiber-type and Barbari goats with meat-type was examined to unravel gene networks and metabolic pathways that may contribute to cashmere development. Functional annotation and enrichment analysis identified significantly enriched pathways such as keratinization, formation of cornified envelope and developmental biology. It was observed that the expression of genes related to keratins (KRTs) and keratin-related proteins (KRTAPs) was much higher in Changthangi goats. A number of transcription regulatory genes involved in hair follicle keratin synthesis, such as ELF5, GPRC5D, PADI3, HOXC13, FOXN1 and LEF1 were upregulated in cashmere producing goats. It was suggested that positive regulation of Wnt signaling pathway and negative regulation of Oncostatin M signaling pathway may contribute to hair follicle development and hair shaft differentiation in Changthangi goats.

Fu *et al*. (2020) investigated the role of lncRNAs and mRNAs in regulating cashmere fineness of Tibetan Cashmere goats. RNA sequencing was performed by taking skin samples from goats with fine-type and coarse-type fiber in the anagen phase. 2.059 candidate lncRNAs (1.589 annotated lncRNAs, 470 novel lncRNAs) and 80 differentially expressed (DE) lncRNAs were identified and their potential targets were predicted. Besides, 384 of 29.119 mRNAs were identified as differentially expressed. Several key genes such as KRT26, KRT28, KRT39, IFT88, JAK3, NOTCH2 and NOTCH3 and a number of lncRNAs including ENSCHIT00000009853, MSTRG.16794.17, MSTRG.17532.2 were shown to be potentially important in regulating cashmere fineness.

Hui *et al*. (2020) investigated the potential effect of miRNAs on cashmere fineness. KEGG enrichment analysis showed that miRNAs significantly enriched progesterone-mediated oocyte maturation, endocytosis, PI3K-Akt and Wnt signaling pathways from other pathways. A total of 27 miRNAs were randomly selected from different genotypes and validated by qPCR. Among these miRNAs, miR-101 was found to negatively regulate cashmere fineness at the lowest rate, while miR-30a-5p and miR-30e-5p negatively regulated it at the highest rate.

Jin *et al*. (2020) genotyped Inner Mongolian cashmere goat and Liaoning cashmere goat which are known for their cashmere yield and Huanghuai goat using Illumina Caprine 50K SNP array and 53.347 single nucleotide polymorphisms (SNPs) were obtained. 222 candidate genes were identified in Inner Mongolia goats and 173 in Liaoning cashmere goats. Several genes such as CSN3, FOXP1, LRRC14, TRPS1, WDR74, SPTLC3, IGF1R, PADI2, WNT10A and were found to be associated with hair follicle development. 20 genes were identified in both cashmere goat breeds. Among the identical genes, WNT10A and CSN3, which are associated with hair follicle development, were potentially involved in cashmere production. Cashmere-related genes were selected and KEGG analysis showed that these genes were clustered in follicle-related pathways. Further analysis showed that these genes were found in pathways regulating stem cell pluripotency, basal cell carcinoma, TGF-β signaling, melanogenesis, Wnt signaling, TNF signaling and PI3K-Akt signaling. The researchers stated that these findings could improve molecular breeding of cashmere goats in the future.

In the study by Su *et al*. (2020), biopsy materials were taken and analyzed in three phases of the secondary hair follicle cycle in Inner Mongolian cashmere goats. There were 29 down-regulated and 22 up-regulated differentially expressed genes (DEGs) in the anagen-catagen phase group, 117 down-regulated and 326 up-regulated DEGs in the catagen-telogen phase group, 582 down-regulated and 197 up-regulated DEGs in the telogen-anagen phase group. As a result of GO and KEGG analyses with differentially expressed genes, FGF5, FGFR1 and RRAS were found to have an impact on the hair follicle growth cycle. The interactive network control chart showed that FGF5, FGFR1 and RRAS are localized to important sites in the MAPK signaling pathway.

Han *et al*. (2018) aimed to determine the differential expression levels of FoxN1, FoxE1 and FoxI3 genes at different periods of fetal development (45, 55 and 65 embryonic ages) and adulthood in Mongolian cashmere goats and to provide new information on genes related to hair follicle development. It has been reported that FoxN1, FoxE1 and FoxI3 genes in the Fox gene family may play a role in hair follicle formation, follicle growth and development.

Zhou *et al*. (2018) tried to determine lncRNA, miRNA and mRNAs that are effective in anagen and catagen phase. lncRNA and miRNA libraries were created by taking biopsy samples from cashmere goats from anagen (September) and catagen (February). 1,122 known and 403 novel lncRNAs were identified, 173 of which were found to be differentially expressed between anagen and catagen. In addition, 3.500 gene-encoding transcripts that are differentially expressed between these two phases were identified. 411 known miRNAs and 307 new miRNAs were identified. Of these, 72 were found to be differentially expressed. It was also known that catagen-inducing factors such as TGFβ1 and BDNF are regulated by miR 873 and lnc108635596 in lncRNA-miRNA-mRNA networks.

Peng *et al*. (2017) carried out the transcriptome analysis of genes expressed in the skin of goats with three different undercoat colors: white, brown, and gray. It was found that the MC1R gene was not differentially expressed in all three coat colors. It was stated that DCT, PMEL, TRPM1 and TYRP1 genes may have an important role in the formation of brown undercoat color, and ELOVL3 and PMEL genes may play an important role in the formation of gray undercoat color. It was stated that the fact that ASIP gene only in goats with white undercoat color seems to be important in the maintenance of this undercoat color, and these results can be used to increase our knowledge in understanding the molecular background involved in the pigmentation of undercoat color.

Conclusion

Angora goat and cashmere goat are two goat breeds that are mainly raised for their fiber. At the same time, Angora goat is in an important genetic resource of our country and cultural heritage. When the existing studies are evaluated, it is seen that there are limited studies to elucidate the molecular mechanisms affecting the quality and quantity of mohair fiber, which are mostly concentrated on increasing cashmere yield and quality, and there is great need for studies in this field. In addition, the studies needed to obtain fine mohair fiber will contribute to the textile industry and rural development in terms of our country. By making animal fiber production sustainable, it will also contribute to the conservation of Angora goat, which is an important genetic resource.

Conflict of Interest

The authors declare that they have no known competing financial or non-financial, professional, or personal conflicts that could have appeared to influence the work reported in this paper.

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