



Review Article

On Hair Follicle Development and Wool Production Traits in Sheep: A Review

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Abstract

Hair follicle and skin development is a complex biological process involving many regulatory molecules. Wool trait is a complex quantitative trait controlled by multiple genes and affected by environment. In this paper, the histomorphology of hair follicle development in sheep and the molecular mechanism of hair follicle and wool traits formation were reviewed in order to provide theoretical basis for breeding and selection of sheep wool traits. © 2021 Friends Science Publishers

Keywords: Sheep; Hair follicle development; Wool production traits; Transcriptome; lncRNA; GWAS

Introduction

Hair is one of the important features of animal appearance. It has a great influence on body beauty, spirit and social psychology. There are some rare hairless animals in the animal kingdom. The morphogenesis of hair follicle is complicated, and several stages are involved in it (Schneider *et al.* 2009). The problems relevant to the key genes (single and/or genes) affecting hair follicle development, together or singly, are worthy of further exploration and analysis. It is a challenge to locate and analyze the molecular basis of sheep wool traits by traditional candidate genes. There exists the question how to improve the accuracy of the selection of wool quality traits and the scientific bases of breeding program in sheep breeding. To answer this, the urgent task is to carry out the research on the molecular basis and regulatory mechanism in the formation process of fine wool quality traits. The present review presents a number of tasks to clarify the phenomenon. Firstly, the histomorphology of skin and hair follicles is described. Secondly, the important molecular genetic progress in sheep skin, hair follicle development and wool production traits by transcriptomics and lncRNA have been systematically described. Thirdly, the genetic variation screening and other molecular means were addressed. The purpose of this review is to provide a scientific theoretical basis for carrying out further studies relevant to fine wool sheep genetics and breeding, wool production traits and wool quality.

Histomorphology of skin hair follicles

As an important accessory organ of skin, hair follicle has its

own unique physiological structure (Chong *et al.* 2003). Though the main structure of hair follicle is same, it varies a little among different species and genera of animals (Paus and Cotsarelis 1999). The duration of hair follicle morphogenesis varies with the animal species. Hair follicle is the skin cell which takes part in the hair growth, development and regeneration of animal fur and plays a significant role in mammals (Zhang *et al.* 2009). After the development of hair follicle, it will grow periodically and renew itself constantly. Therefore, it is a renewable organ. Under the control of various growth factors and molecular regulatory mechanisms, hair follicles continue to undergo a cyclical process of growth, degeneration and rest.

It was reported that sections of Inner Mongolia Albas cashmere goat embryo skin was observed and photographed under the microscope (Zhang *et al.* 2007). The results showed that the hair follicle structure of cashmere goat was composed of hair ball, connective tissue sheath, outer root sheath, inner root sheath and hair stem. Another study on morphological observation on the development of rat embryonic hair follicle showed that the morphogenesis of rat embryonic hair follicle occurred on the 12th day of embryo. And was formed by the cells in the basal layer of epidermis, protruding into the dermis, and there were mesenchymal cells around it (Hao *et al.* 2006). Liu *et al.* (2015) carried out microscopic observation separately on the longitudinal and transverse sections from the skin tissues of Aohan fine wool sheep on the 90th and 120th day of gestational age and lambs on 1 and 30 d after birth, respectively. The results showed that the structure of wool sac of Aohan fine wool included connective tissue sheath, outer root sheath, inner root sheath, hair stem and hair bulb. The above-mentioned results can

provide reference for understanding the changes in morphological structure of fine wool follicles and screening differential genes, related to wool density.

Molecular genetic progress of hair follicle development and wool trait

Research progress of candidate genes and signal pathways related to hair follicle development and wool production trait. The development of hair follicle mainly includes eight stages (Veen *et al.* 1999). The first and second stages of development followed the formation of basal plate and hair root, respectively. The 3-5th stage is the formation of hair nail and the differentiation of hair follicle occurs at the 6-8th stages. Hair follicles are regulated by a variety of molecular signals in different growth cycles (Lin *et al.* 2006). The pathways, promoting hair follicle growth include Wnt/bcatenin, EDA/EDAR, Shh, notch and TGF β . BMP is one of the pathways that inhibit hair follicle growth. Shh is an important regulator in hair follicle development (Fuchs and Raghavan 2002). In the early embryo stage, notch affects the growth and development of hair follicles by stimulating hair follicle stem cells (Kopan and Weintraub 1993). Wnt is a germ plasm secretory protein that controls downstream target genes by interacting with receptors on cell membrane (Jamora *et al.* 2003). Wnt plays an irreplaceable role in the process of hair follicle formation. It participates in all aspects of hair follicle formation and plays a very important role in the development of hair follicles in almost all animals (Jamora *et al.* 2003). BMP family also plays an important role in the early stage of hair follicle development, and BMP4 can inhibit the development of hair basal plate (Blessing *et al.* 1993). Noggin and BMP4 are a pair of antagonists, which can effectively prevent the binding of BMP4 and its receptor and promote hair follicle growth (Botchkarev *et al.* 1999 2002). The expression of Hox gene affects the morphology of hair follicles (Packer *et al.* 2000; Shang *et al.* 2002). EGF is expressed in the outer root sheath of hair follicles and is closely related to the growth and development of keratinocytes (Nanney *et al.* 1984; Cros *et al.* 1992). EGF can delay the development and prolong the growth cycle of hair follicles (Chen *et al.* 2002). FGF and FGF-receptor gene expression in early hair follicle development, promote hair follicle formation. FGF-5 can inhibit the growth of hair follicles and make them enter into the later growth stage (Ota *et al.* 2002). Related research reported that natural length and straight length of wool of modified individual owned two indel in FGF5 gene in adult Merino sheep (GM), were significantly longer than those of wild type (WT) (Hu *et al.* 2017). And the amount of dirty wool was also significantly higher than that of WT individuals. It indicated that FGF5 gene edited by CRISPR/cas9 can promote the growth of wool, thus increasing the length and yield of wool. In addition, the coding region of FGF5 was cloned (Liu *et al.* 2011) and found that FGF5 gene is highly expressed in skin tissues

relative to kidney, small intestine, heart, spleen, liver, pancreas and lung. These evidences further indicate that FGF5 can be used as a candidate gene for hair length selection. TGF β -2 and TGF β -1 belong to TGF family. TGF β -2 can induce hair follicle development, while TGF β -1 can inhibit hair follicle development (Bond *et al.* 1996; Schmidullrich and Paus 2005). Wnt10b can induce immature epidermal cells to differentiate into hair stem and inner root sheath. Wnt10b is highly expressed in hair mother cells and inner root sheath, and promotes the continuous development of hair follicle (Mikkola and Millar 2006). In this concept, the worth mentioning is that MAP2 gene is a key gene responsible for hair follicle density and 1 missense mutation of A-to-G at rs328005415 in MAP2, causing a valine-to-methionine substitution leads to the hairless phenotype (Jiang *et al.* 2019). Kinesin superfamily proteins (KIFs) are a kind of molecular motors, which can combine with adenosine triphosphate (ATP) and convert the chemical energy produced by hydrolysis into mechanical energy. Related research has shown that a SNP was significantly related to the coefficient of variation of wool fiber diameter, which was located on chromosome 13 of sheep and could be identified as Kinesin family member 16B (KIF16b) gene (Wang *et al.* 2014). It is speculated that this gene can be used as a candidate gene for sheep wool traits. Based on the above concept, KIF16b gene family was expected to receive more and more attention in the future. At the same time, it plays a very important role in the process of intracellular material transport, which is responsible for transporting protein complexes, organelles and mRNA along microtubules to its positive electrode key proteins for basic cell activity (Hirokawa and Tanaka 2015). The above-mentioned key genes that affect hair follicle development are worthy of further exploration and analysis.

Progress in transcriptomics of sheep skin

The screening of genes, regulating wool growth provides theoretical guidance for improving wool production efficiency, product quality and breeding, and also provides basis for the development of therapeutic drugs for human hair loss and other symptoms. There have been many studies on genetic polymorphism of wool and cashmere growth and regulation (Purvis and Franklin 2005; Cano *et al.* 2007; Bidinost *et al.* 2008). In mammals, several gene families, such as Wnts, TNFs, FGFs and TGFs, have been found to be involved in hair follicle development and growth (Galbraith 2010). Microarray analysis and other transcriptome studies have been successfully applied to the characterization of mouse hair follicle stem cells (Rhee *et al.* 2006; Janich *et al.* 2011). Microarray studies on different characteristics of sheep and goats, such as breast development (Bongiorni *et al.* 2009), goat milk quality (Ollier *et al.* 2007), hair follicle development (Norris *et al.* 2005), resistance to natural wool rot (Smith *et al.* 2010), and pigmentation of skin and wool (Penagaricano *et al.* 2012)

have been reported. The gene expression patterns of Aohan fine wool sheep's lateral skin and groin skin were compared using gene expression microarray technology and proteomics technology (Liu *et al.* 2014). Results obtained showed 1494 differentially expressed probes, including 602 probes with high expression and 892 probes with low expression. Cluster analysis and gene annotation showed that the differentially expressed genes mainly bind to receptors related to multicellular biological process, protein binding and polymer complex. Using RNA sequencing technology, Zhang *et al.* (2017) studied the skin tissue of Superfine merino wool sheep (SM) and Small tail han sheep (STH) and coarse wool sheep. He obtained 435 differentially expressed genes, including 127 down-regulated genes and 308 up-regulated genes. GO and KEGG enrichment analysis showed that the genes, highly expressed in SM, were mainly related to hair follicle stem cell markers. However, wool fiber composition and lipid metabolism pathway, and genes related to wool fiber structure are mainly concentrated in KRT and KRTAP gene family. On the other hand, the genes highly expressed in STH were mainly related to skin keratinization and muscle composition. Similarly, the research related to miRNAs expression profile in the skin and hair follicles of Liaoning cashmere goat and Aohan fine wool sheep during the stationary period were also surveyed by solexa deep sequencing technology (Li *et al.* 2016). A total of 1910 known miRNAs and 2261 new miRNAs were identified. Among them, 107 newly discovered miRNAs and 1246 known miRNAs were differentially expressed in the two breeds. Go and KEGG enrichment analyses showed that these miRNAs played an important role in hair follicle growth and development. As an important factor in animal breeding, coat color is produced by skin melanocytes and determined by the amount and type of melanin released (Ito *et al.* 2000; Ito and Wakamatsu 2008). In addition, the skin tissues of three white and black wool Sunit sheep were collected and used for transcriptome sequencing, and found 845 new differentially expressed genes (Fan *et al.* 2013). Of which 107 and 738 genes were highly expressed in black sheep and white sheep skin, respectively. And 49 known hair color related genes were expressed in skin tissues, 13 genes were highly expressed in black sheep skin, mainly in DCT, MATP, TYR and TYRP1 which were related to melanin and its receptor. Some important genes function was shown in the Table 1.

Research progress of non-coding RNA in hair follicle development

In the process of hair follicle development and growth cycle, it is regulated by many factors and pathways. Through the influence of these regulatory mechanisms, hair follicles cycle in the process of growth, regression and rest. As an important regulator, lncRNA plays a significant role in hair follicle development. Long noncoding RNA (LncRNA) is a kind of

eukaryotic transcripts with a length of more than 200 nt and noncoding capacity. It is the key regulator of gene coding proteins. It regulates gene expression at both transcriptional and post transcriptional levels. It is widely distributed in animal and plant genomes. As an important regulator, lncRNA participates in life cycle, cell differentiation and some disease-related biological processes. At present, some lncRNAs and miRNAs related to skin biology have been reported. A large number of studies have shown that lncRNA plays an important role in the process of skin hair follicle development, participates in regulating the expression of hair follicle and hair fiber growth related genes. It is closely related to hair follicle development and periodic changes, and can play its biological functions by interacting with many growth factors and signal pathways. Many studies found that 6127 lncRNAs were expressed during the growth and resting stages of cashmere, among which 54 were significantly different (32 up-regulated and 22 down regulated). And targeted knockout of the differentially expressed lncRNA-5479 showed that it was closely related to the growth period of hair follicles and participated in the formation of keratin (Guo 2015; Feng 2016). Moreover, lncRNAs and miRNAs usually work together to occur in primary hair follicle induction of sheep fetal skin (Nie *et al.* 2018). It was also found that 36 of the differentially expressed lncRNAs were up-regulated and 26 were down-regulated. The down-regulated lncRNAs interacted with keratin (krt14 and krt15), BMP signal (sostdc1), Wnt signal (wnt16 and SFRP1) and laminin (LAMA1), which mainly affected the development of epidermis and wool substrate. Additionally, the transcription patterns between resting and growing stages of cashmere goat secondary hair follicles were definituded and found 13 differentially expressed lncRNAs, of which 6 were up-regulated in growth period, and 4 were up-regulated in resting period (Bai *et al.* 2018). The results showed that the expression levels of lncRNA-000133 (Zheng *et al.* 2019), lncRNA-H19 (Zhu *et al.* 2018) and lncRNA-HOTAIR (Jiao *et al.* 2019) in cashmere goat hair follicle development and growth stage were significantly higher than those in resting period. Combined with promoter methylation analysis, the hypermethylation of lncRNA-H19, lncRNA HOTAIR and lncRNA-000133 may be involved in the expression inhibition of Cashmere goat secondary hair follicles. In addition, many studies predicted and identified the target genes of differential lncRNAs in the induction period of secondary hair follicle of fine wool sheep (Liu 2016; Wang *et al.* 2018). Where, it was found that lncRNA may also participate in the regulation of fine wool follicle morphology through nod like receptor signaling pathway, leishmaniasis and NF kappaB signaling pathway occurrence and development cycle.

Research progress on GWAS of sheep wool traits

GWAS refers to the search for single nucleotide variations related to the main economic traits of animals and plants

Table 1: List of some important gene functions

Gene name	Function	Experimental technology	Species	Reference
FAM101A, COL21A1 and FACIT	Dirty wool	SNP50 bead chip	sheep	Ebrahimi <i>et al.</i> (2017)
MAP2	Prenatal hair follicle density	GWAS	pig	Jiang <i>et al.</i> (2019)
PML, LAMC2 and PDGFD	Wool fiber bending properties	OvineSNP50 BeadChip	Chinese Merino sheep	Di <i>et al.</i> (2015)
FGF5	Length and yield of wool	CRISPR/cas9 and RT-PCR	sheep	Liu <i>et al.</i> (2011)
KIF16B	Coefficient of variation of wool fiber diameter	GWAS	Chinese Merino sheep	Wang <i>et al.</i> (2014)
WNT10b	hair stem and inner promotes differentiation of skin epithelial cells.	Cell validation experiment	mouse	Mikkola and Millar (2006)

within the biological genome. Wang *et al.* (2014) used GWAS analysis on the wool yield and wool quality of 765 Chinese Merino sheep and found 28 SNPs sites significantly related to wool fiber diameter, its change rate and fineness and crimp. Gene annotation showed that 43% of SNPs were involved in the biological process of hair growth and development. Moreover, some SNPs were found significantly associated with wool staple crimp frequency, wool length and wool yield in Chinese Merino sheep. Further, it was found that five SNPs related significantly to wool staple crimp frequency which were located on chromosomes 2, 12, 15 and 18, respectively (Di *et al.* 2015). Two SNPs which were significantly related to wool length could be located on chromosomes 2 and 15, and 3 SNPs related significantly to wool yield could be located to chromosomes 6, 7 and 1. Gene annotation and analysis showed that SNPs significantly related to wool staple crimp frequency were located in IKZF2, LAMC2, ARHGAP42, GABRG3 and PML. And SNPs significantly related to wool length and wool yield were located or adjacent to FIBIN, HSD17b11 and PIAS1, which involved in wool growth and development related biological processes. In addition, the amount of dirty wool of 96 Baluchi sheep was used for GWAS analysis by ovine SNP50 bead chip (Ebrahimi *et al.* 2017), and found that three SNPs significantly related at chromosome level were located on chromosome 17 and 20 respectively. Gene annotation revealed that these three loci were located or adjacent to FAM101A, COL21A1 and FACIT.

Conclusion and outlook

Hair follicle development and wool trait have received greater attention in ruminants, especially sheep. At present, the research on transcriptome, lncRNA and GWAS in hair follicle development and wool trait mainly focuses on the screening and identification of candidate genes, lncRNA and genetic variation sites (including SNP and CNV). However, the mechanism of these candidate gene or regulatory molecule is still unclear. With the rapid development of molecular technology and gene editing technology, it is necessary to reveal the molecular mechanism of hair follicle periodic growth more deeply and accurately. It also provides new research direction and ideas for livestock breeding and hair follicle development and wool trait improvement.

Author Contributions

Wu Sun wrote the first draft, Shike Ma designed the experiment and Yuhong Ma revised the text.

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