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The Genetics of Skin Color Variation in Farm Animals

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Review Article

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Abstract

Melanin from melanocytes has a broad spectrum of biological activities, including protection against enzymatic lysis, UV radiation, and damage by oxidants and resistance to drugs by pathogens, protection of insects against bacteria and antiviral protection, etc. Coloration of the hair, skin, and eye in animal depends on the quantity, quality, and distribution of the pigment in tissues. Pigmentation is a variety of phenotypes that is important to husbandry. We reviewed the progress of skin color variation in farm animals to provide insights into the biology of skin pigmentation and melanocyte.

Keywords: Melanin; Skin; Pigmentation; Candidate Gene; Farm Animal

Pigment and its Potential Function

Melanogenesis

Coloration of the hair, skin, and eye in animal depends on the quantity, quality, and distribution of the pigment in tissues. Melanocytes are pigment producing cells of the skin in humans and other vertebrates. Melanocytes originate from the neural crest with pluripotential cells that gradually become lineage specific during development, eventually they become localized in hair follicles as well as in the epidermis to pigment the hair and skin, respectively [1-3]. It is known that melanocyte is not only responsible for synthesis of different types of pigment in melanosomes, but also for the transport of pigment from melanocyte to the surrounding epithelial cell (keratinocyte). Melanins can be produced in two chemically distinct types, black-to-brown eumelanin and yellow-to-reddish-brown pheomelanin by the melanocyte in mammal and bird. The eumelanins are highly insoluble pigments that form within specialized cells known as melanocytes. Enzymatic action of the enzyme tyrosinase on the amino acid tyrosine produces melanin. In their primary biosynthetic pathway, tyrosine is hydroxylated to form the catecholamine 3,4-dihydroxyphenylalanine (DOPA), which is then oxidized to form 3,4-dioxyphenylalanine (dopaquinone) before cyclization to 5,6-indole quinones and their subsequent polymerization to form melanin. Similar to the biosynthesis of eumelanin, melanin known as pheomelanin is biologically synthesized, except that a precursor containing Sulphur is incorporated in the structure. In nature, many biological systems produce a combination of the two types of melanin. In husbandry, pigmentation phenotypes are a kind of important production traits, especially as a distinct marker for certain breed of animals.

Potential Functions of Melanin

It has been reported that melanin from natural sources has a broad spectrum of biological activities, including protection against enzymatic lysis, UV radiation, damage by oxidants, resistance to drugs by pathogens, protection of insects against bacteria and antiviral

protection [3-6]. Melanin also can chelate metal ions and to act as a physiological redox buffer [7,8]. Evidence from Revskaya, et al. [4] and Kunwar A, et al. [5] indicate that melanin from the plant and fungus can provide significant protection against radiation in mice. In addition, melanin can interact with drugs and metals and has certain pharmacological properties. The most significant properties of melanin is its antioxidant effects and enhancement and modulation of the immune system. Recently, other important and valuable characteristics of melanin have been identified, such as modulation of gastrointestinal health, hepatoprotective effects, anti-inflammatory effects, and anti-carcinogenic effects [6].

Candidate Genes for Skin Color in Farm Animals

Chicken

The Silky chicken (Gallus gallus) is the earliest studied and noteworthy for the hyperpigmentation in tissues and organs such as the dermal layer of skin, bone, muscle, pleura, trachea, blood vessels, abdominal lining, and connective tissue. Silky is an exceptional chicken in which numerous melanoblasts travel via a ventral pathway and disperse into internal organs. Finally, these ectopic melanocytes induce heavy dermal and visceral melanization known as Fibromelanosis (Fm). Identification of the candidate gene for Fm locus continued over half of a century, until the breakthrough undertaken by Dorshorst, et al. [7] It has been demonstrated that the causal mutation of Fm is an inverted duplication endothelin 3 (EDN3) gene in genomic regions, which increase expression in EDN3, thus promoting melanoblasts migration and proliferation in early embryonic stage [7]. Interesting, Yu, et al. [8] have identified a novel mutation (c.–1826A>T), associated with the skin color (dorsal and subalar) of black-bone chicken, in the ASIP gene promoter by altering ASIP transcriptional activity [8]. This indicates ASIP participates in the regulation of skin color, which is supported by the recent study in zebrafish and avain [9,10]. Li, et al. [11] used the 600K Affymetrix Axiom HD genotyping array to perform a genome-wide association study on pure lines of 19 Tibetan hens with dermal pigmentation shank and 21 Tibetan hens with yellow shank to refine the Id location. The genome-wide study revealed that 3 SNP located at 78.5 to 79.2 Mb on the Z chromosome in the current assembly of chicken genome (galGal4) were significantly associated with dermal shank pigmentation of chickens, but none of them were located in known genes. The interval we refined was partly converged with previous results, suggesting that the Id gene is in or near our refined genome region [11]. Zhang, et al. [12] investigated the genetic basis of the gray dilution phenotype in the Anti tile-like gray chicken. They found that the allele E of the MC1R gene and FM alleles act together to cause the development of the "five-black" phenotype (black feather, comb, skin, shank, and beak), whereas the MLPH mutation results in defective melanosome transport, leading to the development of the "five-gray" phenotype [12]. In additional, Zhang, et al. [13] mapped the gene responsible for the dermal shank pigmentation in chickens by an association analysis and a differential expression analysis, and found that GRAMD3 could be the most likely candidate gene for the Id locus.

Pigs

The belt pattern can be described as a white band of varying width around the midsection of the body but does not always encircle the body completely, and is considered to result from a lack of melanocytes. Giuffra, et al. [14] confirmed the dominant inheritance of the belt pattern in Hampshire swine and identified the belt locus as the fourth allele at the KIT locus on pig chromosome 8. Fernandez, et al. [15] reported that two OCA2 intragenic haplotypes were associated with skin color variation in Iberian pigs , which provide evidence of a suggestive dominant effect of haplotypes on color intensity and indicate an important contribution of additive polygenic effects (h2 = 0.56 +/- 0.21) to the variance of this trait. The phenotype of ACOP (ambilateral circumocular pigmentation) is characteristic for some breeds of farm animal, such as Rongchang pig and a minority of the FV animals of the Fleckvieh (FV) cattle breed. In areas where animals are exposed to increased solar ultraviolet radiation, ACOP is associated with a reduced susceptibility to bovine ocular squamous cell carcinoma (BOSCC, eye cancer). Interestingly, Chen, et al. [16] found a short insertion in the distal melanocyte-specific regulatory region of MITF creates a de novo silencer that completely eliminated the expression of the transcripts for the MITF-M isoform, which led to observed phenotypes of deafness and skin depigmentation, similar to the phenotype of Waardenburg syndrome in humans. Xu, et al. [17] compared expression profiles of coding and non-coding RNAs from white and black skin in Wuzhishan pigs using high-throughput RNA sequencing method. They demonstrated that key genes such as MLANA, PMEL, TYR, TYRP1, DTC, TRPM1 and CAMK2A had significantly different levels of expression in the two skin tissues, and that a total of 15 lncRNAs, 11 miRNAs and 7 genes formed 23 lncRNA-miRNA-gene pairs, suggesting that complex regulatory networks of coding and non-coding genes underlie the coat color trait in Wuzhishan pigs.

Cattles

Pausch, et al. [18] identified QTL point to MCM6, PAX3, ERBB3, KITLG, LEF1, DKK2, KIT, CRIM1, ATRN, GSDMC, MITF and NBEAL2 as underlying genes for eye area pigmentation in cattle. The twelve QTL regions explain 44.96% of the phenotypic variance of the proportion of daughters with ACOP. The chromosomes harboring significantly associated SNPs account for 54.13% of the phenotypic variance, while another 19.51% of the phenotypic variance is attributable to chromosomes without identified QTL. These support a polygenic inheritance pattern of ACOP in cattle and provide the basis for efficient genomic selection of animals that are less susceptible to serious eye diseases. Color sidedness is a dominantly inherited phenotype of cattle characterized by the polarization of pigmented sectors on the flanks, snout and ear tips. It is also referred to as 'lineback' or 'witrik' (which means white back), as color-sided animals typically display a white band along their spine. Color sidedness is documented at least since the Middle Ages and is presently segregating in several cattle breeds around the globe, including in Belgian blue and brown Swiss. Durkin, et al. [19] reported a novel CNV-generating translocation mechanism involving circular intermediates, namely, color sidedness is determined by a first allele on chromosome 29 (Cs(29)), which results from the translocation of a 492-kilobase chromosome 6 segment encompassing KIT to chromosome 29, and a second allele on chromosome 6 (Cs(6)), derived from the first by repatriation of fused 575-kilobase chromosome 6 and 29 sequences to the KIT locus. Awasthi Mishra, et al. [20] and Rothammer, et al. [21] identified TWIST2 as the candidate gene of the belted phenotype in Brown Swiss. Hofstetter, et al. [22] found a non-coding regulatory variant in the 50-region of the MITF gene is associated with white-spotted coat in Brown Swiss cattle. Zwane, et al. [23] reported that KIT and MITF were associated with skin pigmentation in three South African indigenous breeds (Afrikaner, Drakensberger, and Nguni) using whole genome sequencing.

Sheep and Goats

Penagaricano, et al. [24] identified candidate genes associated with the development of black skin spots in Corriedale sheep, and found that C-FOS, KLF4 and UFC1could be candidate genes associated with the development of black skin spots. Raadsma, et al. [25] identified QTL of 13 skin and fibre pigmentation traits in sheep. A total of 19 highly significant, 10 significant and seven suggestive QTL were identified in a QTL mapping experiment using an Awassi × Merino × Merino backcross sheep population. They revealed that the ovine TYRP1 gene on OAR 2 was a strong positional candidate gene. Up to 47% of the observed variation in pigmentation was accounted for by models using TYRP1 haplotypes and 83% for models with interactions between two QTL probabilities, offering scope for marker-assisted selection for these traits. The Youzhou dark goat is a natural mutant with dark skin over the whole body including the visible mucous membranes in China. We investigated the genetic basis of the skin hyperpigmentation in Youzhou dark goat [26-28]. Our findings suggest that a presumed structure variation (duplication or insertion) in ASIP might be responsible for its lower expression in the hyper pigmented skin (Youzhou dark goat) by determining the distribution of melanocytes across the body at early development stage, suggesting ASIP might be the key candidate gene for the skin hyperpigmentation in You zhou dark goat. In addition, two another interesting pigmentation phenotypes in sheep (Ovis aries) and goat(Capra hircus) have been reported recently, the black-boned sheep and goat, which characterized in hyperpigmentation of the muscle, bone surface (periosteum), kidney, inner skin, heart, lung and trachea, compared with the red coloration in normal animal [29,30]. Deng, et al. [29,31-33] and Jiang, et al. [34-36] investigated that polymorphism of the pigmentation genes and histological characteristics respectively, but the causative genes associated with the hyperpigmentation phenotype in Black-bone sheep and goat remain to be identified further.

Conclusion and Perspective

Unlike the model animal such as mice and rat, there are few melanocyte lines available for further investigations in farm animals, which hinder the further investigation of pigmentation in farm animals. In addition, most investigations of pigmentation phenotypes focus on variation of coat color rather than skin color in the livestock. However, investigations of the skin pigmentation can provide valuable information for human diseases associated with melanin, such as skin melanopathy, melanosis coli, mucosal melanosis, etc. The findings in mice and human may contribute much to our understanding of the genetic basis for skin color variation in farm animals, despite the fact that there are many differences in dermal microstructure between mice and human [37]. Especially, many important and valuable findings from mice in vivo and in vitro are milestones in this topic [38-49]. With the emerge of the state of the art in life science technology such as high throughput sequencing (PacBio and Manopore) and genome edition, it is more and more feasible for people to reveal the

molecular mechanisms underlying the phenotypes of skin color in farm animals.

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