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The Non-Coding RNAs Involved in Physiology and Pathology of Skin Melanocyte and Melanoma

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Review Article

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Abstract

The non-coding RNAs consist of the major of transcripts in genome in higher plants and animals, and they modulate gene expression at multiple levels to affect the growth, development, physiology, and disease in organisms. Recent findings demonstrate that the non-coding RNAs play important roles in physiology and pathology of melanocyte and melanoma. We reviewed the progress in non-coding RNAs (microRNA and long non-coding RNA) involved in pigmentation to provide insights into the melanocyte and melanoma biology.

Keywords: Micro RNA; Long Non-Coding RNA; Melanocyte; Melanoma

Category of Noncoding RNAs

Noncoding RNAs (ncRNAs) are those transcribed but not translated into proteins. According to their function, they are classified into housekeeping RNAs including ribosomal(rRNA), transfer RNA (tRNA), small nuclear RNA(snRNA), small nucleolar RNA(snoRNA), transfer-messenger RNA(tmRNA), guide RNA(gRNA), telomerase RNA and regulatory RNAs such as microRNA(miRNA), piwi-interacting RNA(piRNA), small interfering RNA(siRNA), enhancer RNA(eRNA), long noncoding RNA(lncRNA), circle RNA(cRNA). Alternatively, based on their length, they are also classified into small RNAs (18 to 200 nucleotides) and long RNAs (>200 nucleotides). Among the ncRNAs, miRNA is one group that has been identified earliest and most extensively studied [1-4]. Subsequently, piRNA, which is a class of animal germ cell specific and single stranded RNA molecule (24 to 30 nucleotides), has been found [5,6]. However, the first discovered lncRNAs are H19 and XIST [7-10]. With evolution of species, the count of ncRNA, especially for miRNA and lncRNA, would be increasing as well. In addition, with development of investigation, the biological mechanism of ncRNAs in genome is expanding and enriching as well. Taking miRNA as example, it has been traditionally regarded as negative regulator of gene expression by binding to the 3′untranslated region of a target mRNA, leading to translational inhibition or degradation of protein-coding genes. However, recent evidence shows that miRNA can target various

noncanonical sites such as DNA promoter regions, RNA 5′ untranslated region, other ncRNAs, and proteins, which is far beyond that initially thought. More interestingly, miRNAs can promote protein translational either directly via recruitment of protein complexes, or indirectly unleashing the translation repression. For example, miRNAs can modulate the Toll-like receptor signaling by an agonist effect on Toll-like receptors [11]. It is acknowledged that the ncRNAs are master regulators of transcription, transcript stability, and translation of protein-coding transcripts, with roles in both physiological and pathological processes.

Melanocytes Development and Melanoma

Melanocytes originate from the neural crest with pluripotential cells that gradually become lineage specific during development [12,13], eventually they become localized in hair follicles as well as in the epidermis to pigment the hair and skin, respectively [14]. 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. In nature, many biological systems produce a combination of the two types of melanin. The extracellular signals control the type of melanin produced by melanocyte including ASIP/α-MSH/MC1R, SCF/c-Kit, ET-1/ETBR, Wnt/β-catenin, bFGF/FGFR, HGF-cMET, GM-CSF/GM-CSFR, PGs/PGR, NGF/NGFR, LIF/gp130LIFRα,DKK1/LRP, TGFβ1/TβR, NO/cGMP, and sex hormones (i.e., androgen, estrogen) pathways [15]. Defects in melanocyte development and function are associated with a variety of human diseases and disorders, whereas the cancerous growth of melanocytes can results in melanoma. Melanoma is one of the most aggressive human skin cancer and some sub-type is highly resistant to treatment. Until now, there are more than 378 loci in mouse (171 cloned and 207 uncloned genes) involved in tissue pigmentation (http://www.espcr.org/micemut/), of which transcription factors such as MITF, PAX3, and SOX10 play crucial regulatory roles in cell commitment, migration, survival, and differentiation of the melanocyte [16]. Besides the above protein-coding genes already described, recent evidence indicates that non-coding RNAs, such as micro RNA and long noncoding RNA, play crucial roles in melanocyte and melanoma biology.

MicroRNAs

Since Wu, et al. [17] for the first time reported the role of miR-434-5p in regulation of human skin color, a large number of miRNAs related to melanogenesis have been identified. Recently, Mione, et al. [18], Mirzaei, et al. [19], Ross, et al. [20] made comprehensive reviews about the role of miRNAs in melanogenic process. For example, one group of miRNAs including miR-15b, miR-21, miR-99a, miR-137, miR-145, miR-148, miR-149, miR-193b, miR-194, miR-203, miR-205, miR-206,miR-211,miR-221/22,miR-214,let-7a/b,miR-506-514 and so on are involved in cell growth and proliferation. The other group of miRNAs including miR-18b,miR-26a,miR-34a,miR-34b/c,miR-100,miR-155,miR-125b,miR-137,miR-149,miR-203,miR-4286, miR-205, et al. participate in cell apoptosis. Another group of miRNAs such as miR-214,miR-30b/30d,miR-182,miR-126,miR-137,miR-196a,miR-18b,miR-34b/c,miR-199,miR-211,miR-9, miR-31, et al. are related to cell survival, invasion and metastasis. However, most of these reports are derived from the melanoma in human, few studies are conducted in normal melanocyte. Recently, there are only 3 miRNAs (miR-155 [21], miR-9 [22], miR-2909 [23]) identified in human melanocytes. Findings from Dong C and his colleagues in ShanXi Agricultural University found miR-25, miR-101a-3p, miR-144a-3p, lpa-miR-nov-66, miR-143-5p, and miR-5110 play important roles in alpaca melanocyte migration, proliferation and melanogenesis [24-28]. Zhang, et al. [29] identified a miRNA in embryonic chicken retinal pigment epithelium and showed that the protective effects of alpha-MSH may be due to the MC4R mediated-down-regulation of miR-194 during the glutamate-induced excite toxicity. Our team have recently identified some miRNA involved in skin pigmentation in goat, such as miR-381, miR-543, miR-544, miR-129, and miR-29a [30,31]. We summaries these studies in Table 1, which can contribute with a better knowledge about microRNAs involved in epigenetic regulation of melanogenesis.

miRNAs	Roles in cell process	Cell source
miR-10b[32-55],miR-15b, miR-18a-5p, miR-21, miR-99a, miR-106a, miR-137, miR-145-5p, miR-148, miR-149, miR-193b, miR-194, miR-203, miR-205, miR-206, miR-211, miR-221, miR-222, miR-214, let-7a/b/c, and miR-506-514, miR-140-5p, miR-150-5p, miR-154, miR-431, miR-142, miR-146a, miR-217, miR-224-5p, miR-136, miR-135b, anti-miR-1297, miR-28-5p, miR-495-3p, miR-1224-5p, miR-1297, miR-155, miR-126-3p, miR-507	cell growth and proliferation	melanoma
miR-18b,miR-26a-5p[56,57],miR-34a,miR-34b/c,miR-100, miR-150-5p[42], miR-155,miR-125b,miR-137,miR-149,miR-203, miR-4286, and miR-205, miR-126[58], miR-494[59], miR-590-5p[60-62], miR-383, miR-497-5p, miR-195-5p and miR-455-3p	cell apoptosis	Melanoma, retinal pigment epithelial
let-7b/c[39], miR-10b[32,63], miR-18a-5p,miR-214,miR-30b/30d,miR-182, miR-137,miR-196a,miR-18b,miR-34b/c,miR-199,miR-211[36],miR-9, and miR-31, miR-140-5p, miR-150-5p[41], miR-154[43-45], miR-431, miR-142, miR-146a, miR-150-5p[42], miR-224-5p[48], miR-136[49], miR-135b[50], miR-28-5p[51], miR-199a-3p[64], miR-122-5p[65], miR-455-5p, miR-495-3p, miR-1224-5p[66], miR-145-5p[35], miR-222[37], miR-205[67], miR-126-3p[54], miR-507[55]	cell survival, migration invasion, and metastasis	melanoma
miR-625-5p[68]	melanoma cell glycolysis	melanoma
miR-25[24], lpa-miR-nov-66[26], miR-143-5p[27], miR-5110[25] , miR-101a-3p and miR-144a-3p[28]	melanocyte migration, proliferation	Alpaca skin melanocytes
miR-155[21], miR-9[22], miR-2909[23]	cell survival, adhesion migration, mitochondrial respiration	human primary melanocytes
miR-194[29]	cell death and tissue damage	embryonic chicken retinal pigment epithelium
miR-381[30],miR-543[30], miR-544[30], miR-129[30], miR-29-5p[31]	melanogenesis, melanocyte migration	goat skin melanocytes

Table 1: The category of microRNAs based on their roles in melanocyte and melanoma cell.

Long Non-Coding RNAs

There is a body growing of evidence which suggests that the long non-coding RNAs (lncRNAs) play important roles in modulation of melanocyte biology. In order to explore the molecular mechanism underlying the early skin pigmentation, we identified recently a large number of skin lncRNAs associated with melanogenesis by Illumina RNA sequencing in two different color of fetal skin in goats and investigated their basic characteristics and the genome-wide cis-/trans- actions [69]. However most of database of lncRNAs already described as involved in pigment as deposited in human melanoma database. Based on the mechanisms underpinning the regulation of melanogenesis, we classify them into two groups. Some lncRNAs affect melanoma occurrence and invasion, and melanoma cell behavior through modulation of the protein-coding genes, such as GAS5 [70], NUMB [71], PAUPAR [72], SAMMSON [73], SLNCR1 [74], ANRIL [75], CANT1 [76], PVT1 [77], HOXD-AS1[78], MT1JP[79], TUSC7[80], LINC01260 [81], H19 [82], MEG3 [83], ILF3-AS1 [84], GAS5 [85], RMEL3 [86], SNHG7 [87], NEAT1 [88], SNHG17 [89], HAND2-AS1 [90], SLNCR [91], MIAT [92]. For example, the results of Li, et al. [83] suggested that MEG3 can inhibit melanoma development through blocking Wnt signaling pathway. Schmidt, et al. [91] demonstrated that SLNCR recruits AR to EGR1-bound genomic loci and switches EGR1-mediated

transcriptional activation to repression of the tumor suppressor p21(Waf1/Cip1), which implicate the regulatory triad of SLNCR, AR, and EGR1 in promoting oncogenesis and may help explain why men have a higher incidence of and more rapidly progressive melanomas compared with women.

Others of lncRNAs function as a sponge competing endogenous RNA (ceRNA) for miRNA, such as UCA1 [51, 55], HOXA11-AS [93], CCAT1 [94], MALAT1 [57,95], MEG3 [96], ATB [60], CASC2 [33], SNHG5 [56], NEAT1 [97], TUG1 [98], ZEB1-AS1 [66], OIP5-AS1 [47], ZFAS1 [42], DSCAM-AS1 [49], FOXD3-AS1 [99], MIR205HG [100], MIAT [100], and AK077216 [61]. For example, Lu, et al. [93] demonstrated that HOXA11-AS, which is overexpressed in UM tissues and cells, could simultaneously interact with enhancer of zeste homolog 2 (EZH2) to suppress its target p21 protein expression. HOXA11-AS also functioned as a molecular sponge for miR-124, and overexpression of miR-124 attenuated the proliferation and invasion-promoting effect of HOXA11-AS. In addition, Wang, et al. [101] identified 5 candidate ceRNA(AC068594.1, C7orf71, FAM41C, GPC5-AS1, MUC19, LINC00402) by integrative analysis of lncRNAs, miRNA and mRNA expression in metastatic melanoma. Like the relationship between miRNA and mRNA, a lncRNA can act as a sponge for two miRNAs simultaneously, such as UCA1 vs. miR-28-5p and miR-507 [51,55], MALAT1 vs. miR-34a and miR-183 [57,95]. Interestingly, some lncRNA can act as a positive regulator of microRNA but not as a microRNA sponge in regulation of melanocyte biology. For example, Cheng, et al. [37] found miR-222 is positively regulated by HMGA1. Moreover, the proliferation and migration of UM cells significantly increased in the miR-222 mimics group and decreased in the miR-222 inhibitor group. The p-PI3K, p-Akt and MMP9 expressions were elevated in UM cells transfected with miR-222 mimics, and suppressed in the miR-222 inhibitor group. In addition, there is an interaction between two lncRNAs in melanoma. For example, Huang, et al. [102] revealed that lncRNA LINC-PINT is down regulated in melanoma and may regulate melanoma cell proliferation by down regulating lncRNA BANCR. These studies substantially enlarge the function profiles of lncRNAs in melanocyte and melanoma biology. We summarized the regulatory mechanisms already described of lncRNAs in melanoma biology in Table 2. There still could be other novel modes of action in lncRNAs to be identified in future.

LncRNAs	mechanisms of lncRNA
GAS5 [70],NUMB [71-92], PAUPAR, SAMMSON, SLNCR, ANRIL, CANT1, PVT1 , HOXD-AS1, MT1JP, TUSC7, LINC01260, H19, MEG3, ILF3-AS1, GAS5, RMEL3, SNHG7, NEAT1,SNHG17,HAND2-AS1, SLNCR, MIAT	Direct modulation of protein-coding genes
UCA1 [51,55], HOXA11-AS [93], CCAT1 [94], MALAT1 [57,95], MEG3 [96], ATB [60], CASC2 [33], SNHG5 [56], NEAT1 [97], TUG1 [98], ZEB1-AS1 [66], OIP5-AS1 [47], ZFAS1 [42], DSCAM-AS1 [49],FOXD3-AS1 [99],MIR205HG [100], MIAT [100], (AC068594.1, C7orf71, FAM41C, GPC5-AS1, MUC19, LINC00402) [101], AK077216 [61]	Function as a sponge and competing endogenous RNA (ceRNA) for miRNA
HMGA1 [37]	Function as positive regulator of miRNA
LINC-PINT and BANCR [102]	Interaction between two lncRNAs

Table 2: The category of lncRNAs based on the regulatory mechanism in melanocyte and melanoma biology.

Conclusion

In summary, non-coding RNAs play important roles in physiology and pathology of melanocyte and melanoma. According report by the ECODE (Encyclopedia of DNA Elements) project, 76% of human genome is selectively transcribed, and only less than 3 % of human genome are been translated into proteins eventually [103]. These non-coding RNAs consist of a large network that modulates gene expression at multiple levels. The non-coding RNAs mentioned above (Figure 1) are just the tip of the ice berg; the main part of it still remains under the sea. Especially, with the development of high throughput sequencing technology, i.e. whom genome sequencing (WGS), and the state of the art long reads sequencing such as PacBio and Nanopore, more and more new noncoding

RNAs involved in melanocyte and melanoma would be readily identified to elucidate the molecular mechanisms underlying the phenotypes of skin pigment in human and animals.

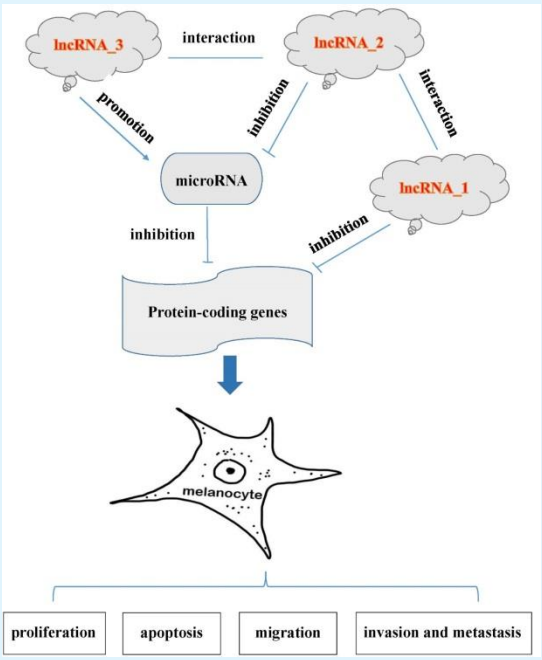

Figure 1: Sketch of the mechanisms of microRNA and lncRNA in melanocyte and melanoma.

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