Published in final edited form as:

Exp Dermatol. 2015 November ; 24(11): 821–826. doi:10.1111/exd.12785.

MicroRNAs (miRNAs) in the control of HF development and cycling: the next frontiers in hair research

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Abstract

Hair follicle development and its postnatal regeneration are characterized by dramatic changes in its microanatomy and cellular activity, which are controlled by multiple signalling pathways, transcription factors and epigenetic regulators, including microRNAs (miRNAs). miRNAs and their targets form remarkably diverse regulatory networks, playing a key role in the execution of gene expression programmes in the different cell lineages of the hair follicle. This review summarizes the roles of miRNAs in the control of hair follicle development, cycling and hair pigmentation, emphasizes the remaining problems/unanswered questions, and provides future directions in this rapidly growing and exciting area of research.

Keywords

development; hair cycle; hair follicle; microRNA

Introduction

The hair follicle (HF) is a skin appendage, in which tightly coordinated interactions between cells of different origins (epithelial, mesenchymal and neuroectodermal) result in the generation of an organ-specific product, a pigmented hair fibre (1). HF development and its postnatal regeneration are characterized by dramatic changes in its microanatomy and cellular activity, which are controlled by multiple signalling pathways, transcription factors and epigenetic regulators (2–6). The HF undergoes cyclic transformation and transits through the distinct phases of resting (telogen), active growth (anagen) and regression (catagen). HF structural remodelling is associated with a timely activation of stem cells, balanced proliferation and differentiation of their progenies, switching on and off of melanogenesis, and coordinated apoptosis (5,7–9). Hair cycle-dependent changes in the

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Author contribution

All authors contributed to the design and writing of the manuscript and approved the final version.

Conflict of interests

The authors declare no conflicting interests.

follicular micro-anatomy are governed primarily by the WNT, TGF-β/BMP, hedgehog, EDAR, FGF and IGF signalling pathways (10–15).

However, protein-coding genes constitute of a very small fraction of the total amount of mammalian DNA, while the vast majority of the human transcriptome is represented by non-coding RNAs. The different subfamilies of non-coding RNAs control gene expression by regulating chromatin architecture, transcription, translation and RNA turnover among others (16). It has recently been demonstrated that several long non-coding RNAs, such as TINCR and ANKR, are involved in the control of epidermal differentiation and stratification (17,18). However, the roles for long non-coding RNAs in HF development and growth remain largely unknown.

On the other hand, small non-coding RNAs especially micro-RNAs (miRNAs) are better understood. miRNAs are small single-stranded RNA molecules, which are only about 22 nucleotides in length. They control gene expression at the post-transcriptional level by changing mRNA stability, promoting mRNA degradation and negatively impacting translation (19). The biogenesis of miRNAs is a complex process (reviewed in (20)). In the canonical miRNA biogenesis pathway, miRNAs are transcribed by RNA polymerase II, which results in the generation of a long primary transcript (pri-miRNA) with a local hairpin structure. Pri-miRNA transcripts are processed by the Drosha–DGCR8 microprocessor complex, to form an approximately 70-nucleotide precursor miRNA (pre-miRNA), which is exported into the cytoplasm by exportin-5. Pre-miRNAs are processed further by another RNAseIII enzyme Dicer into approximately 22-nucleotide-long mature miRNA duplexes consisting of the guide and passenger strand. The guide strand is incorporated into a miRNA-induced silencing complex (miRISC), recognizes target sites in the 3′ untranslated region (3′UTR) through its ‘seed sequence’ (nucleotides 2–8) and induces mRNA degradation, and inhibition of translation.

It has been estimated that between 30% and 80% of the protein-coding genes may be regulated by miRNAs (21). An individual miRNA may interact with an entire set of genes, while the expression of a single gene may be controlled by multiple miRNAs. Thus, miRNAs are involved in the regulation of diverse biological functions during development, differentiation and pathological conditions (19,22,23). In this review, we summarize the roles of miRNAs in the control of HF development, cycling and hair pigmentation, emphasize the problems/unanswered questions, and provide future directions in this rapidly growing and exciting area of research.

Everything you always wanted to know about miRNAs (but were afraid to ask)

Before we explore the importance of miRNAs for HF biology, we would like to further address additional and very basic questions relating to miRNA function. This will enable us to highlight current limitations in our understanding of miRNA biology and how studying the role of individual miRNAs in the context of skin biology may fundamentally contribute to progress in answering some of these questions:

- Why are miRNAs so abundant?
- How many targets does a miRNA really have?
- Is the seed sequence the dominant interaction sequence to determine the target gene?
- Which area(s) of the target mRNA really contain(s) the binding site? The 3′ UTR dogma and canonical versus non-canonical sites (the seed sequence dogma).
- How much does a miRNA affect expression of the target gene?
- How important are miRNA expression changes?

Why are miRNAs so abundant?

What is mysterious about miRNAs is their huge number. Currently, there are over 2500 mature human miRNAs in miRBase, release 20. What is the reason for such a large number of posttranscriptional regulators? It has been speculated that there is a relationship between miRNA number and organismal complexity. Although the number of protein-coding genes is surprisingly ‘stable’ between complex and less complex organisms, it can be speculated that miRNAs have been key players in extending the number of cell and tissue types. Indeed, miRNA profiling studies in the HF during morphogenesis and cycling revealed the spatiotemporal expression of a large number of miRNAs (24–26), which indicates the significance of miRNAs in gene expression regulatory circuits of a complex mini-organ such as the hair follicle. It is safe to say that a complex structure such as a HF may be difficult to achieve without miRNAs. And indeed, as we will highlight in the following sections, miRNAs are essential for HF development and hair growth.

How many targets does a miRNA really have?

Despite many years of intensive research into target genes of miRNAs, this issue is not resolved. Initial and serious attempts to address this question indicate that miRNAs can regulate on average at least 7 (27) to up to 100 genes (28). In 2005, at a time when only a few hundred of the most abundant miRNAs were known, Bartel’s group estimated that over 5000 human genes are likely miRNA targets and, indeed, target sites may not be restricted to the 3′UTR (29). Experiments with miRNA knockout or their overexpression indicate that the impact of the loss of a miRNA can be broad. For example, complex changes in the HF and skin morphology induced by miR-125b overexpression were associated with the repression of over 800 transcripts, which were predicted to be conserved miR-125b targets (26). However, there is also some justification to focus on a very few key target genes (30). Recent years have brought tremendous progress in regard to target gene assays, which significantly help us to improve our knowledge of the nature of target genes and their number.

Most likely, the major take-home lesson here is that the abandonment of the one miRNA–one target gene–one phenotype blunder should be substituted with a more complex systems biology-inspired approach.

Is the seed sequence the dominant interaction sequence to determine the target gene?

This question deals with the topic of the so-called 8-nucleotide-long seed sequence (23), which is indeed important for many target interactions (31).

However, intensive studies in Drosophila by Brenneke *et al.* (28) showed that targeting does not need to involve a classical seed sequence. This may explain why a miRNA is normally around 20 nucleotides long and not just around 8 nucleotides. Therefore, the inconvenient answer is that there may be a much more complex targeting pattern when we generally take into consideration and that there are many more 'non-canonical' targets that we should study (32,33). Therefore, this issue is still controversial despite recent comments in Nam *et al.* (34) that '…noncanonical site types are either not effective or less effective than 6-mer sites', with 6-mer sites by far the least effective canonical sites, and the clarification of the structural importance of the seed sequence for miRNA function and target recognition (35).

Which area(s) of the target mRNA really contain(s) the binding site(s)?

Now, where to look for the binding sites of miRNAs in mRNAs? Although initial studies indicated that miRNAs preferentially target the 3′UTR of mRNAs (22,36), these studies generally looked only for classical seed matches (8 mers). Since then, things got more complicated and a tentative answer is that one can expect that miRNAs will target sequences outside the 3′UTR, including 5′UTR and the coding region of their target gene (37–41). However, the overall relevance of these non-canonical target sites especially for ancient and highly conserved miRNAs awaits further studies and clarification.

How much does a miRNA affect expression of the target gene?

The rule of thumb here is to talk in percentages rather than fold changes. The majority of experiments indicate that one can expect a change in expression of the average target gene on the mRNA and protein level of 20–50%. Taken into account that these numbers only reflect the loss of function, one can assume – including dramatically increased expression of the miRNA – a rough total range starting at 40%. These numbers may be very different for individual targets and are intended to give the reader a rough idea.

How important are miRNA expression changes?

Let's assume the expression level of a miRNA was to remain absolutely the same, for example, during keratinocyte differentiation, but the transcriptome changed: How would this affect the target gene spectrum of the miRNA? This little mind exercise is intended to show the complexity of the system. However, recent data suggest that the overwhelming majority of target genes is the same whether you look into cell type A or cell type B (34). This is to some extent surprising considering the vast amount of literature that has accumulated on many different cell types: frequently, different target genes for the same miRNA are favoured over others despite the fact that the target gene spectrum is very similar between cell types. A major contributor to differences in the miRNA target spectrum between different transcriptomes is mediated by alternative polyadenylation (34).

Another aspect of the question relates to the idea that miRNAs may function as 'buffers' of gene expression. How important is the concentration of the buffer within a certain range?

Does it matter if a miRNA varies twofold for a buffering function? Is a 50-fold change of a lowly expressed miRNA more important than a 1.5-fold change of the top expressed miRNA? These questions are of utmost importance as comparisons of miRNA expression patterns and levels are the starting point for most miRNA-related projects and eventually scientific publications. One of the best examples could be a study by de Pontual *et al.* (42), which demonstrates that haploinsufficiency in *MIR17HG* (a twofold change in miRNA expression) causes Feingold syndrome 2 associated with severe developmental abnormalities.

In short, all these can be summed up with a conservative rule from a more dogmatic point of view: miRNAs preferentially bind to the 3′UTR region of a mRNA, with the most effective and functional sites recognized be the 8-mer seed. This will result in a change in expression of the set of target genes of about 15–40% on the mRNA and the protein level. This can also be used by the cell to suppress unwanted transcripts. These transcripts may cause ambiguous signals and initiate processes that are not appropriate (initiation of cell division, differentiation, cell fate change, etc.). To fulfil their functions, miRNA expression levels can fluctuate to a certain degree without having tremendous impacts on target gene expression as binding sites are in general overrepresented compared to miRNA levels (43,44). Therefore, to identify disease-or process-related miRNAs, it seems wise to select the ones that are massively altered between two states *and* have a substantial expression level in one of the states.

With this background information, we would now like to summarize our current knowledge of the functions of miRNAs in HF biology (Table 1).

miRNAs and their role in the control of hair follicle development and cycling

Indispensable roles for miRNAs in the development and organogenesis have been demonstrated by cell-specific or tissue-specific interferences with miRNA biogenesis. In the skin, constitutive surface ectoderm-specific deletion of miRNA processors *Dicer* or *Dgcr8* during embryonic development (E14.5–E17.5) results in the severe abnormalities in HF development characterized by the inability of the hair follicles to invaginate into the dermis, which leads to major structural defects and failure to produce a hair shaft (25,45,46). Consistently, the ablation of the vital components of RISC components Ago1 and Ago2 also leads to marked changes in skin morphogenesis, including the formation of HF cysts (47).

Naturally, miRNAs are essential not only for HF development, but also for its postnatal growth. When Drosha or Dicer is deleted after HF initiation has been completed (at E18 or P1), fully developed hair follicles (P12-P14) exhibited abundant apoptosis in the hair matrix and structural changes in the hair shaft, which eventually led to HF degradation (48). In summary, these studies have provided striking evidence on how global loss of miRNAs in the embryonic epithelium dramatically changes the molecular interactions between epithelial and the dermal cells resulting in the failure to form a normal hair follicle, and on how miRNAs are required in adult hair follicles for proliferation and apoptosis control.

Individual miRNAs exhibit unique spatio-temporal expression in the developing and cycling hair follicle. Differential enrichment in miRNAs in the cells of epidermal and HF lineages can be detected as early as day 17 of mouse embryonic development (25). These differences in miRNA expression profiles in the different epithelial lineages of the skin are believed to contribute to the establishment of these very same lineages. Even within the hair follicle, major differences in miRNA expression are evident between the bulge, outer root sheath (ORS) and hair matrix cells, while surprisingly high similarities were observed between the miRNA profile of the bulge and basal epidermal cells (26).

miRNAs and hair follicle stem cells

To follow our view that highly expressed miRNAs are generally the important miRNAs in a given cell type, we would like to start our exploration of individual miRNAs with miR-205. miR-205 and miR-203 can be regarded as *the* squamous epithelial miRNAs (25,45,49). Yi and colleagues have demonstrated that miR-205 is highly enriched in the epithelial progenitors and stem cells during skin development. They have also shown that it is vitally important for HF development (30). The deletion of miR-205 results in severe developmental defects and a perinatally lethal phenotype, which is very rarely seen in miRNA knockout mice. miR-205 promotes stem cell expansion during early HF development and its ablation negatively impacts proliferation of stem cells and their direct progeny, while not exhibiting an effect on highly proliferative hair matrix cells. This study confirmed miR-205 as an important regulator of the PI(3)-kinase signalling (50) and as a HF stem cell activator that is crucially important for HF morphogenesis (30).

miR-125b is also preferentially expressed in progenitor cells in the epidermis and HF (26). It has been shown that miR-125b acts as a repressor of HF stem cell differentiation, and therefore indispensable for anagen onset (26). Indeed, aberrant expression of miR-125b in the outer root sheath leads to an expansion of stem-like cells with their impaired capacity to differentiate, which eventually leads to the development of alopecia. Interestingly, vitamin D receptor (VDR) serves as one of the critical target genes of miR-125b in follicular cells, and decreased VDR levels explain several of the defects in HF differentiation in miR-125b transgenic mice (26).

This role of miR-125b is consistent with its functions in regulating the activity of different stem cell types outside of the skin, including embryonic stem cells (51), hematopoietic stem cells (52) and neural stem/progenitor cells (53). Screening for miR-125b targets in human, mouse and zebrafish cells revealed that miR-125b controls stem cell homoeostasis by buffering and fine-tuning p53 network activity and by regulating the expression levels of both proliferation and apoptosis regulators (54). In addition, miR-125b may regulate proliferation in stem cells which may be inhibited by TGF-β/activin/BMP signalling; miR-99a/100~125b tricistrons regulate hematopoietic stem and progenitor cell homoeostasis by shifting the balance between TGF-β and Wnt signalling (55). This suggests that miR-125b may function not only by maintaining stemness in HF stem cells, but also is involved in maintenance of their lineage-specific phenotype via targeting lineage-specific genes beyond VDR.

miRNAs and hair matrix proliferation

Remarkably, epithelial deletion of Dicer or Drosha from adult telogen skin did not have a major effect on hair follicles nor the epidermis (48). However, the loss of these miRNA-processing enzymes resulted in severe abnormalities in the rapidly proliferating matrix keratinocytes of anagen hair follicles. Dicer or Drosha knockout mice show increased apoptosis and DNA damage in hair matrix keratinocytes (48). These observations provide clear evidence that rapidly proliferating keratinocytes are highly sensitive to the global miRNA loss.

The previously mentioned miRNA profiling studies revealed that individual miRNAs are expressed in the postnatal skin in a cell-type- and hair cycle-dependent manner. For example, telogen and anagen hair follicles show striking differences in their miRNA expression levels giving important clues on which miRNAs may be important for the regulation of proliferation and apoptosis (24).

Among different miRNAs, miR-31 and miR-214 are abundantly expressed in the proliferating hair matrix keratinocytes and the outer root sheath during anagen (24,56). Pharmacological inhibition of miR-31 in mouse back skin promotes anagen and results in the appearance of hair shaft defects (24). MiR-31 exhibits its effects on hair growth, at least in part, via modulating the activity of BMP and FGF signalling pathways, as well as via changes in the expression of structural proteins such as keratin 16 and keratin 17 (24).

In contrast to miR-31, Krt14-driven overexpression of miR-214 results in the growth of smaller and shorter anagen hair follicles associated with reduced proliferation in the hair matrix. Inhibitory effects of miR-214 on hair growth were mediated by targeting the activity of the Wnt and Shh signalling pathways (56).

Therefore, these miRNAs, miR-31 and miR-214, are essential for anagen maintenance, and they provide strong evidence for the concept that miRNAs highly expressed in proliferating cells are crucial for maintaining a balance between proliferation, differentiation and apoptosis. Interestingly, miR-214 is involved in the control of Wnt signalling pathway in the HF by targeting β-catenin (56), while β-catenin, in turn, has been shown to be capable of directly regulating Dicer1 expression in brain cells (57). These data suggest a feedback loop between Wnt signalling and global miRNA-mediated post-transcriptional gene regulation. However, the functional significance of β-catenin/Dicer1/miRNA interactions in skin remains unexplored. Further investigations into the interactions between the Wnt pathway and miRNAs in keratinocytes will help to better understand the complexity of Wnt-dependent regulation of HF development and cycling.

miRNAs and hair follicle differentiation

Another highly expressed skin miRNA is miR-24. miR-24 is involved in the regulation of differentiation programmes in HF development and is predominantly expressed in the differentiated keratinocytes of the inner root sheath (58). Constitutive overexpression of miR-24 in proliferating cells during skin morphogenesis leads to abnormal HF development associated with reduced proliferation and premature differentiation. It was discovered that Tcf3 acts as one of the targets of miR-24 (58). Tcf3 is the transcription factor expressing in

the follicular stem cells and their progenies in the outer root sheath to maintain their undifferentiated state (59,60). Therefore, the lack of miR-24 expression in proliferating cells contributes to the maintenance of their proliferative activity. miR-24 was also implicated in the control of differentiation of other cell types, including epidermal keratinocytes (61), hematopoietic cells (62) and muscle cells (63). E2F2 was identified as one of the critical miR-24 targets (64). Taken together, miR-24 is the only miRNA so far found to be exclusively expressed in the inner root sheath to govern HF differentiation during anagen phase.

miRNAs and hair follicle pigmentation

Production of a pigmented hair shaft by the HF occurs as the result of functional interactions between follicular melanocytes, keratinocytes and dermal papilla fibroblasts, which form a HF pigmentary unit. The formation of the HF pigmentary unit begins during embryogenesis when melanocytes migrate from the neural crest into the skin and populate the individual developing hair follicles (65,66). The fully formed HF pigmentary unit consists of three melanocyte populations based on their status of differentiation: undifferentiated melanocyte progenitors located in the follicular bulge, the differentiating melanocytes of the ORS, and differentiated pigment-producing melanocytes of the hair matrix (8). Active melanogenesis is strictly coupled to the anagen stage of the hair cycle (67). The control and activity of pigmentation involves multiple growth factors, such as SCF, endothelin 1 and 3, WNT, BMP and hormonal regulation, including POMC-derived peptides, CRH and urocortins (8,66,68–70).

Microphthalmia-associated transcription factor (MITF) is a master regulator of melanocytes and plays a crucial role in their development, proliferation, survival and differentiation by controlling the expression of multiple genes (71,72). Mice with mutations in the microphthalmia (mi) locus lack melanocytes (73). MITF targets key enzymes involved in melanogenesis, such as tyrosinase, tyrosinase-related protein 1 (TYRP1), TRP-2 (which is also called dopachrome tautomerase – DCT) (74) and several other genes involved in melanosome biogenesis, structure and transport (75).

In addition to the long list of known MITF target genes, Dicer was also added as a gene whose expression is directly driven by MITF (76). Dicer is primarily expressed in the differentiated melanocytes of the hair follicle. Melanocyte-specific Dicer deletion leads to melanocyte depletion and results in unpigmented hair. These data demonstrate an essential role for Dicer in the control of melanocyte survival (76).

An additional link between MITF and miRNAs was established by screening for MITF-dependent miRNAs. MITF knockdown in primary melanocytes resulted in upregulation and downregulation of several miRNAs, suggesting their potential involvement in skin and hair pigmentation (77). Still, the strongest candidate for a ‘melano-miR’ is miR-211, whose expression is promoted by MITF (78–80). Indeed, sequencing studies revealed the increased levels of miR-211 in brown versus white alpaca skin, and in the black versus white hair follicles of the goat (Capra hircus) (81,82). How miR-211 is involved in HF pigmentation remains unclear. Several miRNAs have been identified which can regulate melanogenesis by targeting MITF, including miR-340, mir-137, miR-182, miR-25 and miR-218 (83–87).

However, so far miR-137 is the only miRNA affecting hair pigmentation *in vivo*. Transgenic mice overexpressing miR-137 displayed different hair colours which were depended on the levels of miR-137 in the skin (88). Mice with the highest levels of miR-137 produced grey hair, while moderate elevation of miR-137 resulted in the appearance of a brown coat. These phenotypical changes were associated with decreased protein levels of MITF and its target genes tyrosinase, Trp1 and Trp2 (88). Unfortunately, the mouse model of Dong *et al.* does not drive miR-137 transgene expression specifically in melanocytes and may actually mediate its effect on pigmentation through the dermal papilla or follicular epithelium. Furthermore, the normal expression pattern of miR-137 in the HF remains undetermined. Also, we still do not know whether miR-137 affects melanocyte migration during early stages of morphogenesis, or their survival and differentiation, or all of the above.

miRNAs and hair follicle regression (catagen)-associated apoptosis

Apoptosis plays an essential role for proper HF cycling and the maintenance of homoeostasis (9). Different cell populations in the HF exhibit different susceptibility to apoptosis: highly proliferative matrix keratinocytes and pigment-producing melanocytes are sensitive to pro-apoptotic or stress stimuli and dermal papilla fibroblasts are more resistant to apoptosis. Discordance in apoptosis during the hair growth cycle can ultimately lead to either HF degradation, hair loss or a prolonged anagen phase [reviewed in (7)].

Studies with targeted Dicer and Drosha deletion clearly demonstrated the importance of miRNAs for the protection of HF cells against apoptosis, because mutant hair follicles undergo massive apoptosis (45,48). However, we do not know yet the identity of individual miRNAs responsible for the abundance of apoptosis observed in Dicer and Drosha mutant hair follicles.

Teta *et al.* (48) proposed that miR-205 may play a protective role against apoptosis in the hair follicle. In epidermal Drosha and Dicer mutants that show reduced miR-205 levels, they observed increased mRNA levels of the miR-205 target gene E2f1. Because it has been shown that *Krt5* promoter-driven overexpression of E2f1 leads to the elevated apoptosis in the hair matrix (89), it is tempting to speculate that miR-205–E2f1 interactions could be at heart of the control of proliferation and apoptosis in hair matrix keratinocytes (48).

It is well established that p53 is implicated in regulation of apoptosis in the HF keratinocytes. Catagen induction and apoptosis are significantly reduced in the skin of p53 knockout mice (90). Also, p53 knockout mice displayed resistance to chemotherapy-induced apoptosis and did not develop hair loss (90). p53 triggers apoptosis by transcriptional activation of various proapoptotic genes, including Bax, Noxa and Puma, or by repression of anti-apoptotic genes, such as survivin. An increase in Bax expression and downregulation of survivin occurs in catagen (9,91). p53 acts as a positive regulator of the expression of miRNAs. As such, p53 could directly activate miRNA genes (92). p53 can also influence miRNA maturation by interfering with the assembly of a Drosha and p68 (DDX5) complex (93). However, how p53 itself is regulated by miRNAs remains largely unknown. The exploration of a miRNA/p53 feedback circuitry associated with the HF growth cycle could bring a new understanding of the molecular mechanisms controlling catagen.

miRNAs and hair follicle mesenchyme

Unfortunately, we cannot provide much exciting information in this chapter. The area of miRNA-mediated gene expression regulation in the HF mesenchyme (dermal papilla and perifollicular connective tissue sheath) remains largely underinvestigated. All discoveries about the impact of miRNAs on HF development and cycling were made based on the *in vivo* deletion of miRNA-processing enzymes in keratinocytes, while the consequences of miRNA loss in the follicular mesenchyme have not been explored yet.

Therefore, many intriguing questions await answers. How do individual miRNAs contribute to the maintenance of inductive properties of the dermal papilla, its resistance to apoptosis and its remodelling throughout the hair growth cycle? The only study that has started to address the function of miRNAs in mesenchymal components of the HF has compared miRNA expression between balding and non-balding dermal papillae. They discovered four differentially expressed miRNAs. However, the functional significance of these findings remains elusive (94). And although differences in expression may be important, we cannot emphasize enough the importance of absolute expression levels, which was not clarified by Goodarzi *et al.* (94).

Many more studies will be needed to further delineate the significance of functional miRNA–mRNA interactions in HF biology. This will provide new and important insights into fundamental mechanisms that regulate cellular activity and cell fate decisions inside and outside of the skin. Eventually, these findings will be highly important for the development of novel miRNA-based drugs and therapies.

Acknowledgments

This study was supported by the grant from the National Institute of Arthritis and Musculoskeletal and Skin Diseases, part of the National Institutes of Health, under Award Number (5 R01 AR061474-05) to T. Andl, and the Medical Research Council UK (MR/K011324/1) to N.V. Botchkareva.

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Table 1

MicroRNAs involved in hair follicle development and cycling

microRNA	Expression in hair follicle	Target genes	Effects on HF	Reference
miR-125b	HF stem cells	Vdr, Blimp1	Repressor of stem cell differentiation	(26)
miR-137	*unknown*	*Mitf*, *Tyr*, *Trp1*, *Trp2* (*need to be validated*)	Overexpression leads to the hair depigmentation	(88)
miR-24	Inner root sheath	Tcf-3	Antiproliferative, promotes HF keratinocyte differentiation	(58)
miR-205	HF stem cells	Inpp4b, Frk, Phlda3, Inppl1	HF stem cell expansion: stem cells and their progenies' proliferation	(30)
miR-214	HF matrix, outer root sheath	Beta-catenin	HF spacing, matrix proliferation	(56)
miR-31	HF matrix, outer root sheath	Fgf10, keratin 16 and 17, and Dlx3	Inhibition of anagen progression, hair shaft differentiation	(24)