HHS Public Access

Author manuscript

J Invest Dermatol. Author manuscript; available in PMC 2015 March 30.

Published in final edited form as:

J Invest Dermatol. 2013 June ; 133(6): 1450–1452. doi:10.1038/jid.2012.511.

The many paths to alopecia, with compromised hair stem cell regeneration

Ji Li[1,2,3,4], **Ting Xin Jiang**[2], and **Cheng Ming Chuong**[2]

[1]Department of Dermatology, XiangYa Hospital, Central South University, Changsha, Hunan, China

[2]Department of Pathology, University of Southern California, Keck School of Medicine, Los Angeles, California, USA

[3]Center for Molecular Medicine, Xiangya Hospital, Central South University, Changsha, Hunan, China

[4]The State Key Laboratory of Medical Genetics, Institute of Medical Genetics, Central South University, Changsha, Hunan, China

Abstract

Alopecia can be caused by defective formation or increased destruction of hair follicles. Much work has elucidated the control of alopecia caused by regenerative problems due to morphogen signaling. Recently investigators started to reveal nuclear pathways required for the activation and progression of hair stem cells. Taken together these studies will provide new clues to the design of therapeutic strategies.

Alopecia, or hair loss, can be caused by decreased formation or increased destruction of hair follicles. As in many organs, formation defects can result from failure in induction, morphogenesis, or differentiation. However, hair organs are unique in that they undergo regenerative cycling under physiological conditions to renew the worn appendages and to accommodate the animal to its physiological needs at different stages of life (Chuong et al., 2012). The hair cycle involves cyclic activation of hair stem cells and the subsequent reformation of hair organs. While regenerative cycling gives hair organs a new lease on (organ) life, it also opens a new dimension where things can go wrong, leading to an alopecia phenotype. To be able to manage alopecia, we will need to know more about the molecular control of hair stem cells. Much work has been done on the roles of morphogen signaling (wnt, FGF, BMP, etc) in hair stem cell activation from within or outside of the hair follicles (recently reviewed in Hsu and Fuchs, 2012, Chen and Chuong, 2012). However, less has been done to elucidate nuclear events which control stem cell activation to form hair germs, progression of stem cells into transient amplifying proliferating cells, and differentiation to form hair follicles. Given the recent rapid breakthroughs in epigenetics (Botchkarev et al., 2012; Ezhkova et al., 2011), the field is poised to develop new

CONFLICT OF INTEREST

The authors state no conflict of interest.

understanding in the nuclear control of hair regeneration. Alopecia, the easily identifiable phenotype in humans and in mouse mutants (Shimomura and Christiano, 2010) will help us sort out these core pathways. Some new papers report that keratinocyte specific deletion of transcriptional co-activators give rise to progressive alopecia phenotypes(Beverdam et al., JID in press; Nakajima et al., JID in press), but in very different ways. In one paper, hair follicle stem cells were easily activated but quickly became depleted. In a second paper, there was an over abundance of hair follicle stem cells which could not differentiate.

MED (mediator) is a multi-protein co-activator complex that works with transcription factors and nuclear hormone receptors. MED1 (mediator complex subunit 1) is one of the subunits which is known to interact with vitamin D receptors. Keratinocyte specific MED1 ablation showed aberrant epidermal differentiation and hair cycling defects (Oda et al., 2012). These authors report that deletion of MED1 led to increased proliferation of inter-follicular epidermis, accompanied by the increased expression of a supra-basal keratinocyte differentiation marker. They also observed an alopecic phenotype in mutants resulting from rapid regression of hair follicles in the first hair cycle. The penetrance of phenotypes was incomplete. Mutants still formed some hair fibers. While the formed hair fibers were thinner, histological examination showed a lack of proper hair filament differentiation. They compared mutant and control mice at 10 weeks and 6 months of age. Interestingly, they had a paradoxical observation that mutant skin exhibited more hair follicles in anagen at the stages examined, but there were fewer hairs present. They conclude that MED1 deletion leads to abnormal hair follicle anagen activation and defective hair differentiation

Independently, Nakajima et al also engineered mice with a keratinocyte specific MED1 ablation (they used a K5 cre, while Oda et al. used a K14 cre). They also observed hyperplastic interfollicular epidermis that was thicker. Most interestingly, they shaved the skin and were able to observe regenerative hair cycling behavior in living mice (Plikus and Chuong, 2008), instead of examining small regions which sample events as a snapshot. This approach answers the puzzling results observed by Oda et al. 2012. In the first two hair cycles, mutants and wild type littermates were indistinguishable. After that, the cycling behavior of hair follicle population started to become asynchronous. In the normal mice, telogen can be from 12- 60 days long, depending on the stochastic activation of hair follicle stem cells affected by signals intrinsic and extrinsic to follicles. Thus self-organizing regenerative hair wave patterns emerge (Plikus et al., 2011). In the MED1 deficient mutants, follicles synchronously entered the third anagen only 7 days after the second telogen and continued to cycle rapidly. Young mutants appeared to have accelerated hair cycling which later progressed to alopecia phenotypes where hairs were sparse in mice older than 6 months.

To study this phenomenon further, authors used depilation to induce synchronized anagen in a large region of the skin. They then followed the status of hair regeneration in living mutants and in the control. In control mice, hair follicles were induced synchronously, and began* anagen 15 days after depilation. After that, hair cycling became asynchronous and the hair wave resumed. In the mutants, the anagen activation cycle remained synchronized for an additional 3 cycles, and in each cycle telogen was very short. About 100 days post-depilation, hairs became sparse and hair follicles now were in telogen stage, as if they had

exhausted themselves. To explore the mechanism underlying MED1 deletion in hair stem cell homeostasis, the authors used molecular markers and FACS analyses using antibodies against CD34 and integrin α6. They found the number of hair stem cells was similar in 3-week-old mice, but decreased in the mutant mice 2 months old and thereafter. Expression of K15 and Sox 9 confirmed this decrease. These studies led the authors to suggest that MED1 is required to keep hair follicle stem cells and epidermal stem cells in a quiescent stage. In the regenerative cycling of hair follicles, depletion of MED1 leads to accelerated activation of hair follicle stem cells, which eventually lead to exhaustion of stem cells and alopecia. Another potential cause is the dermis. Mutants showed thinner dermis which was a non-autonomus effect. Since regenerative hair cycling was also affected by the extra-follicular environment (Plikus et al., 2011; Chen and Chuong, 2012), the abnormally thin dermis may also have a role in this accelerated activation.

The importance of co-activators in hair cycling is not alone. The Hippo pathway has been suggested to regulate organ size. Downstream to Hippo is YAP (Yes-associated protein), which upon Hippo phosphorylation is blocked from entering the nucleus. In the absence of Hippo mediated phosphorylation, YAP enters the nucleus andworks as a transcriptional co-activator to activate genes with oncogenic potential. Zhang et al. 2011 showed YAP was present in embryonic epidermis, but entered the nucleus less frequently as skin matured. A mutant form of YAP (S127A) was mis-expressed in the mouse skin with increased nuclear localization and YAP activity. Mutant skin showed a thickened epidermis and abnormally evaginated hair follicles in development. Characterization showed increased epidermal proliferation with suppressed differentiation. Beverdam et al., 2012 focused their study on hair follicles. They showed phosphorylated YAP in the hair bulge. They then mis-expressed a YAP mutant (YAP2-5SA-ΔC), in the keratinocyte using a K5 promoter. The mutant YAP protein lacked the normally phosphorylated serine residue and the protein COOH terminus. The skin of these mice appeared normal at birth. Epidermis was thickened with hyper-proliferation and hyperkeratosis. Expression of the epidermal progenitor marker P63 expanded within the epidermal layer.

Hair follicles were initially normal, but progressive alopecia gradually developed at 4–5 weeks of age, and hair loss was obvious by P85. Sebaceous glands were hyperplastic and the outer root sheath was also thickened. Dermal papillae were present, but many of them were not “wrapped” by the epidermal matrix. Some proximal follicles formed abnormal cellular matrix, probably resulting from a failure of proper interactions with the dermal papilla. With alopecic phenotypes, one expected to see the depletion of stem cells like the MED1 deficient hair follicles. Characterization with stem cell homeostasis markers showed the opposite finding! They found cells in the bulge area expressed Keratin15, LHX2, CD34, SOX9. P-Cadherin was expressed but those cells also expressed CD34. Therefore, progression from stem cells to hair germs could not proceed normally. Thus the authors conclude that over-expression of this mutated YAP leads to severe expansion of the hair follicle stem cell / progenitor compartment which, however, were not able to progress to hair germs and subsequent hair follicle organogenesis. Thus progressive alopecia appeared.

The progressive alopecia phenotype is seen frequently when the pathogenesis involves activation of hair stem cells. In another recent study, keratinocyte specific (K14 was used in

this case) deletion of DNA methyltransferase 1 (DNMT 1) mutants showed a normal appearance in newborn mice, but then exhibited a progressively decreased density of hair fibers. By 6 months, there were significant alopecic phenotypes which continued to progress as mice aged (Li et al., 2012). Analyses showed a gradually increased telogen duration and aged skin showed an increased percentage of telogen follicles. Molecular characterization showed K15 and CD34 were in the normal range, but CD200, a hair germ marker, decreased significantly in the mutant. With depiliation, hair stem cells could respond and regenerate, albeit the process took longer. Thus, the problem appears to be due to a failure of hair germ formation from stem cells, not a lack of stem cells. Thus proper DNMT1 activity is required in the process of stem – hair germ cell conversion.

The progressive nature of these alopecia may reflect the stochastic nature of the process of stem cell activation (Plikus et al., 2011). Since the activation of hair stem cells is a decision that integrates multiple inputs of activators and inhibitors, the anagen-reentry behavior of a follicle population has to be described in terms of probability, rather than as a yes or no decision. Cycle after cycle, gradually more and more hair follicles failed to enter anagen and the alopecia phenotype became apparent. Indeed, androgenetic alopecia in humans is also progressive in nature. A recent study suggests that stem cells in the bald scalp of an androgenetic alopecia patient appeared to be normal but the formation of the hair germ was defective (Garza et al., 2011). Extra-follicular factors must be involved since it is age and sex dependent (Chuong et al., 2012). However, genetic predisposition obviously also plays a key role (Shimomura and Christiano, 2010). As more factors involved in nuclear pathway are revealed with rapid progress in genomic related research, we will find more transcription factors, co-activators, epigenetic enzymes and chromatin organizers involved in keratinocyte differentiation and hair stem cell activation (Botchkarev et al., 2012). This new knowledge will help us understand the many pathway involved in hair stem cell activation; intra- or extra-nuclear, intra- or extra-cellular, and intra- and extra-follicular factors, as well as how they crosstalk. The road map will help us design appropriate therapeutic strategies for different types of alopecia (Chueh et al., in press).

ACKNOWLEDGMENTS

JL is supported by the grants from the National Natural Science Foundation of China (NO. 81171520, 81271775). CMC and TXJ are supported by US NIH grants AR42177 and AR 060306. We thank Drs. Sung Jan Lin, Chi-Chiang Chen and Randall Widelitz for discussion.

References

Beverdam A, Claxton C, Zhang XM, et al. YAP controls stem/progenitor cell proliferation in the mouse postnatal epidermis. In press.

Botchkarev VA, Gdula MR, Mardaryev AN, et al. Epigenetic regulation of gene expression in keratinocytes. J Invest Dermatol. 2012; 132:2505–2521. [PubMed: 22763788]

Chen CC, Chuong CM. Multi-layered environmental regulation on the homeostasis of stem cells: the saga of hair growth and alopecia. J Dermatol Sci. 2012; 66:3–11. [PubMed: 22391240]

Chueh SC, Lin SJ, Chen CC, et al. Therapeutic strategy for hair regeneration: Hair cycle activation, macro-environmental modulation, wound-induced follicle neogenesis and stem cell engineering. Expert Opinion on Biological Therapy. In press.

Chuong CM, Randall VA, Widelitz RB, et al. Physiological regeneration of skin appendages and implications for regenerative medicine. Physiology (Bethesda). 2012; 27:61–72. [PubMed: 22505663]

Ezhkova E, Lien WH, Stokes N, et al. EZH1 and EZH2 cogovern histone H3K27 trimethylation and are essential for hair follicle homeostasis and wound repair. Genes Dev. 2011; 25:485–498. [PubMed: 21317239]

Garza LA, Yang CC, Zhao T, et al. Bald scalp in men with androgenetic alopecia retains hair follicle stem cells but lacks CD200-rich and CD34-positive hair follicle progenitor cells. J Clin Invest. 2011; 121:613–622. [PubMed: 21206086]

Hsu YC, Fuchs E. A family business: stem cell progeny join the niche to regulate homeostasis. Nat Rev Mol Cell Biol. 2012; 13:103–114. [PubMed: 22266760]

Li J, Jiang TX, Hughes MW, et al. Progressive Alopecia Reveals Decreasing Stem Cell Activation Probability during Aging of Mice with Epidermal Deletion of DNA Methyltransferase 1. J Invest Dermatol. 2012 Sep 20.

Nakajima T, Inui S, Fushimi T, et al. Roles of MED1 in Quiescence of Hair Follicle Stem Cells and Maintenance of Normal Hair Cycling. J Invest Dermatol. 2012 Aug 30.

Oda Y, Hu L, Bul V, et al. Coactivator MED1 ablation in keratinocytes results in hair-cycling defects and epidermal alterations. J Invest Dermatol. 2012; 132:1075–1083. [PubMed: 22189783]

Paus R, Cotsarelis G. The biology of hair follicles. N Engl J Med. 1999; 341:491–497. [PubMed: 10441606]

Plikus MV, Chuong CM. Complex hair cycle domain patterns and regenerative hair waves in living rodents. J Invest Dermatol. 2008; 128:1071–1080. [PubMed: 18094733]

Plikus MV, Baker RE, Chen CC, Fare C, de la Cruz D, Andl T, Maini PK, Millar SE, Widelitz R, Chuong CM. Self-organizing and stochastic behaviors during the regeneration of hair stem cells. Science. 2011; 332:586–589. [PubMed: 21527712]

Shimomura Y, Christiano AM. Biology and genetics of hair. Annu Rev Genomics Hum Genet. 2010; 11:109–132. [PubMed: 20590427]

Zhang H, Pasolli HA, Fuchs E. Yes-associated protein (YAP) transcriptional coactivator functions in balancing growth and differentiation in skin. Proc Natl Acad Sci U S A. 2011; 108:2270–2275. [PubMed: 21262812]