PLOS Science Wednesday: Hi Reddit, I'm Zhengquan Yu, here to talk about my recent PLOS Genetics paper that has identified the key role of a microRNA in hair loss. I'm joined by Maksim Plikus, who studi

PLOSScienceWednesday [1] and r/Science AMAs[1]

[1]Affiliation not available

April 17, 2023

Abstract

Hi Reddit, My name is Zhengquan Yu and I am an associate professor at the China Agricultural University. Joining me in this AMA is my colleague, Maksim Plikus from the University of California, Irvine, who studies the principles and mechanisms of adult stem cell regulation using hair follicle as the primary model system. My research focuses on regulatory network of somatic stem cells in hair follicle and mammary gland. We recently published a research article titled Post-transcriptional Regulation of Keratinocyte Progenitor Cell Expansion, Differentiation and Hair Follicle Regression by miR-22 in PLOS Genetics. We describe an essential role for a highly conserved microRNA, miR-22, in regulating the regression of mouse hair follicles. We found that increasing miR-22 results in hair loss in mice due to the premature regression of follicles, and that silencing of keratin-mediated hair shaft assembly by miR-22 is a prerequisite for follicle regression. There are hundreds of microRNAs expressed in hair follicles, but most of them are not well studied. This paper highlights the importance of determining the combinatorial effects of the microRNA regulatory network in hair cycling and provides new insights into the mechanism of premature hair follicle regression in understanding the pathology of hair loss. We will be answering your questions at 1pm ET (10 am PT, 5 pm UTC), Ask Us Anything!

the WINNOWER

REDDIT

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PLOSSCIENCEWEDNESDAY R/SCIENCE

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Since hair loss is generally an age-related phenomenon, does miR-22 increase in presence over time, or is there a mechanism that becomes less resistant to miR-22?

Are you testing any way to reduce the concentration of miR-22 to see if hair loss can be prevented?

BTW, really cool study. My balding friends and family applaud you.

ironmaven
Yes. We found that the level of miR-22 increases in the aged skin. However, we don't know the mechanism whereby miR-22 is induced in response to aging yet.
In mouse model, we did find that loss of miR-22 retards hair follicle regression, which can prevent hair loss or prolong hair growth stage. We are testing this finding in human now.

Could this research lead to growing back hair that has already been lost?

mind_pirate
Maksim: Recent studies showed that dormant hair follicles in patients with androgenetic alopecia

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maintain their key stem cell population. Please refer to this study: http://www.ncbi.nlm.nih.gov/pubmed/21206086

This suggests that as long as the signaling mechanism of androgenetic alopecia pathogenesis can be interrupted, dormant scalp hair follicles can regrow. For instance, this 2003 study showed that grafting of vellus human scalp follicles onto mouse partially restores their normal growth characteristics: http://www.ncbi.nlm.nih.gov/pubmed/12734505

Do you believe the findings of your research could pave the way for better treatments for hair loss?

BeansAndBacon156
Zhengquan: I think that our findings provide a new therapeutic target to treat hair loss in way of microRNA. The cause of hair loss is pretty complex, it is hard to develop effective treatment for all patients. However, inhibition of miR-22 could benefit a certain number of patients whose hair loss caused by increasing miR-22.

MiR-22 has been shown to be upregulated in certain cancers, such as prostate cancer, and downregulated in several other cancers. Is there any link between balding and prostate cancer that you know of, and to what extent do you think that hair loss is a result of mechanisms that might by and large be protecting us from cancer? Thank you for doing this. Very interesting!

ReverendAI
Zhengquan: This is a great question. You raise a good point. Actually, baldness was associated with increased risk of prostate cancer. Please check this following link if you want know more information. http://news.discovery.com/human/health/balding-check-for-prostate-cancer-too-130328.htm. It has been reported that miR-22 is upregulated in prostate cancer and promotes tumorigenesis by targeting tumor suppressor Pten. Thus, miR-22 might be the common cause of hair loss and prostate cancer.

Hi there. I started balding at the age of 19 but thanks to propecia, I still have a full head of hair 8 years later.

My question is, the constant bombardment of DHT at a certain point can cause inflammation by constantly overstimulating the androgen receptors. This causes immune response inflammation if you are genetically sensitive, which causes itching, redness, scaring and shrinking of the follicles, causing miniaturisation and eventually hair loss.

My question is; *why do some boys start balding in their early teens but some men start balding in their 50-60s?*

I mean their both susceptible to MPB yet one experiences it decades early/later. I'm guessing that dht can be equated to a genetic ticking "bomb" in which at some point in a mans life it'll trigger (in essence tell) the follicle to die?

MajesticShadow104
Maksim: Etiology of Androgenetic Alopecia (AGA) is known to be complex and involves factors other than androgen hormones. Genetic factors and metabolic syndrome contribute to it and partially explain the differences between the alopecia onset age. For instance, genetic variance in androgen receptor (AR) was shown to be a major determinant of androgenetic alopecia onset. It is also a X-linked trait, meaning inheritance occurs from the maternal line. Please refer to this 2005 study: https://www.ncbi.nlm.nih.gov/pubmed/15902657

Does this give the possibility of manipulating hair growth?

TheBigWaterBottle
Zhengquan: In our work, we found that increasing miR-22 represses newly hair regeneration and self-renewal of hair follicle stem cell, so inhibition of miR-22 could be helpful for manipulating hair growth.

I was recently reading a paper saying that plucking hairs in a coordinated manner can promote hair regrowth around the damaged area by quorum sensing. The idea was a keratinocyte that is damaged by plucking will release CCL2, and this CCL2 will recruit macrophages which release TNF-α, which in turn promotes hair growth in the area. I think hair growth in each defined area went up by 5-fold.

The authors haven't proposed any mechanism by which TNF-α is having this effect so do you think TNF-α is working by the same pathway as miR-22? Is there a role for inflammation in your pathway or any potential for crossover? I have read that Foxn1 works via PKC to promote keritinocyte differentiation, and there is interplay between TNF-α and PKC. I'm a retrovirologist so not entirely up-to-date with signalling pathways, but it's just a thought.

scientistthrowaway23
Maksim: I am the co-author on the "quorum sensing" study that you are referring to. You are right that the exact signaling mechanism by which TNF-α activates new hair cycle is not fully delineated. However, it involves NF-κB signaling. Please see this quote from the study: "...For example, Tnf-α is known to stimulate both JNK and NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cell) signaling. It is also known that activation of the FGF signaling pathway can trigger hair regeneration (Greco et al., 2009). We therefore screened inhibitors of NF-κB, JNK, PI3K, FGF receptor, p38 MAPK, and Erk for effects on plucking-induced hair regeneration. Only NF-κB inhibitors delayed hair regeneration, doing so by 10 days (Figures 6H and S7C)..."

Tnf-α is released by macrophages and it is an inflammatory cytokine. In that sense, plucking initiated mini-inflammatory response. Generally, inflammation is known to stimulate hair cycle activation. For instance, hair follicles commonly start to grow at the edges of skin wounds, which create inflammatory signaling environment.

Could inhibition of miR-22 through non-genetic means/manipulation, maybe an Anti-miRNA oligonucleotide be used to decrease concentration/expression, and lead to prolonged follicle "life"?

Also are there any environmental factors that could contribute to an increased expression? ROS, UV, etc.

ActiveConcepts
Zhengquan: Yes. miR-22 antagomir or other anti-miR-22 oligonucletides could be used to inhibit miR-22 function, which would prevent hair loss or maintain prolonged follicle life.

As I know, UV exposure can induces miR-22 expression.

Hi, I majored in law in college, so please forgive my scientific illiteracy. I'd like to know is this study means that inherited hair loss is a genetic disorder and incurable?

BTW: 于教授，您用的是名字的拼音又不是英文名，干嘛还要把姓放到后面来？

sywanjw0
Zhengquan: I would say that it is hard to treat inherited hair loss. However, if we could find out which gene is mutated and which signal pathways is affected, we could design and develop some drugs to

prevent hair loss.

So is it treatable with antimir?

Tobikaj
Zhengquan: Yes. It is treatable. Antagomir is easy to penetrance into tissues and could be developed to be a drug. As I know, antimir drugs for miR-122 and miR-34 have been in clinic trials.

When can we expect this to be available to consumers?

60daygoal
Zhengquan: It is hard to say now.

Now that you guys have found positive results in mice, what is the next step? Testing humans?

Wkbrdnjoe
Maksim: Mouse findings would certainly have to be validated in humans. Currently, pilot testing on human hair follicles is possible using two experimental approaches: (i) organotypic hair follicle culture, and (ii) human-on-mouse xenografts. Anagen phase hair follicles, including human follicles, can continue to grow in vitro under specialized culture conditions for approximately one week. Human hair follicles grafted on immune compromised mice can grow for many month, imitating their normal, long-lasting anagen phase. Both approaches are widely used in human hair follicle research.

Importantly, human hair follicles significantly differ from mouse in terms of signaling regulation. For instance, while human hair follicles are highly sensitive to androgen signaling, mouse follicles are not. Therefore, mice can not recapitulate the pathogenesis of human androgenetic alopecia.

Would this help people with alopecia?

not_not_dead
Zhengquan: I believe so. Based on this study, miR-22 antimir could be an effective drug for hair loss.

What inspired you both to pursue this area of study?

Marzhall
Zhengquan: Up to 60% of men experience some degree of hair loss in their lifetime. However, despite its prevalence, efficient treatment for hair loss is lacking. We are eager to understand signaling regulation network of hair follicle, which will provide a better understanding of the hair loss pathogenesis mechanism and identify novel and effective therapeutic targets.

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I've always heard that if your mother's father was bald (or wasn't), you'll be bald as well (or won't be). Is there any truth to this?

twowaysplit
Maksim: Genetic factors of androgenic alopecia are complex. One of them, the variance in androgen receptor (AR) was shown to be a determinant of alopecia onset. It is also a X-linked trait. See this study: https://www.ncbi.nlm.nih.gov/pubmed/15902657

However, there is definitely more to it, and other genetic determinants were found on autosomes. Here are just some relevant studies: https://www.ncbi.nlm.nih.gov/pubmed/17256155 https://www.ncbi.nlm.nih.gov/pubmed/21073542 https://www.ncbi.nlm.nih.gov/pubmed/18304493 https://www.ncbi.nlm.nih.gov/pubmed/22032556

I'm only 22, but my hair started receding about 2 years ago, and now doing so at an accelerating pace. Is there anything I can do to stop it? .....It's very depressing.

leo813
Maksim: There are treatment options available for hair loss. Please schedule to see your dermatologist. Remember that only licensed dermatologist will be able to properly diagnose the type of your alopecia and prescribe appropriate treatment. Some hair loss drugs require doctor's prescription.

Is your progress limited only to hair loss, or could it find applications in other areas?

Considering how much money there aparantly is to make for hair loss treatment, ate you getting companies contacting you left and right offering job positions with large paychecks yet?

hak8or
Zhengquan: In addition to hair loss, inhibition of miR-22 conversely promotes hair growth, so it could be used to enhance hair production in livestock though generating miR-22 knockout goat.

I am 21 and am currently balding substantially. I went from having thick hair to thin hair in the front of my head. What are the steps I can take now, that will ensure hair growth or stop the follicles from regression? Also, what does the hyper thalamus and thyroid gland have to do with hair loss?

ccf91
Maksim: I recommend to see a Dermatologist. Only board-certified medical professional will be able to provide you with the proper medical advice and suggest appropriate treatment. There are several drugs for hair loss available on the market, and some of them require doctor's prescription.

What is your overall view of the pathology of androgenetic alopecia (AGA)? We know from the 50's by the studies of Hamilton that both androgens and genetics are a prerequisite for AGA to occur. The signals upstream are basically Androgens > AR as you know. Lately many studies and researchers are pointing out ROS or DNA damage. Let's call it "stress" which leads to an altered cell fate in the dermal papilla (DP) niche. DP size has been shown to correlate with hair follicle size and thus a reduction of this niche could lead to the miniaturization as we see in AGA. Also it is hypothesized that an altered DP niche might lead to a disruption of the mensenchyme-ephithelial communication and that could explain the lack of progenitor cells in AGA. Studies have furthermore also pointed out that DP cells which are treated with DHT express microRNA which are implicated in cell fate decision (1).

Now there seems to be also another smaller side of a camp that argues that AGA might be the result of prostaglandins doing it's work. Namely the reasoning that PGD2 is overexpressed in scalp and prostaglandins acts highly upstream in the chain of androgenetic alopecia.

- **So what is your own view of the pathology of AGA? Do you concur with something of the above or do you have a other opinion?**
- **Also what is your general opinion of using a rodent model to explain insights in pathologies of hair loss? We have seen from many compound trials that mice seem to grow hair from basically anything. It almost never translates to in vivo results which are applicable to human.**

(1). http://www.ncbi.nlm.nih.gov/pubmed/25778683

Thank you in advance!

Swoopingg
Maksim: your knowledge on androgenetic alopecia already appears to be pretty extensive. As you can appreciate, it has a complex mechanism, therefore many if not all factors that you mentioned are probably involved in its pathogenesis. What is important is to figure out which ones are upstream and which are downstream. This would affect the therapeutic potential of the targets.

As I already mentioned in another reply, rodents and mice specifically, are not an appropriate model for studying androgenetic alopecia. Mouse hair follicles grow very differently from human scalp follicles. Mouse dorsal hairs grow only for about 2 weeks and attain 0.7-1cm in length. This is equivalent to human scalp vellus hair. Moreover, mouse follicles do not respond to androgens the same way human follicles do, and mice do not develop androgenetic alopecia in response to testosterone treatment. This limited the research progress in androgenetic alopecia field. However, we now have organotypic culture system and human-on-mouse xenograft model that can be used for studies on human follicles.