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MANAGING HAIR LOSS

What has research revealed about the pathogenesis of androgenetic alopecia, alopecia areata, and central centrifugal cicatricial alopecia as well as new potential therapeutics?

Feature

By Alison Evans, assistant managing editor, September 1, 2021

To those outside the world of dermatology, hair is sometimes perceived to be a cosmetic concern. Dermatologists know better. With a high psychosocial burden and limited or no treatments approved by the FDA for most hair loss disorders, hair loss is a big deal. Patients with hair loss disorders sometimes move down scale through a multitude of treatments — and even still — may only have partial or no response.

This month in *Dermtitorial*, dermatologists hair loss experts discuss advances in the pathogenesis and treatments for androgenetic alopecia, alopecia areata, and central centrifugal cicatricial alopecia (CCCA).

Androgenetic alopecia

For both male and female pattern hair loss, a certain percentage of hair follicles miniaturize and form tiny hairs that are essentially microscopic, said George Cotsarelis, MD, FAAD, the William Burke Ramsay professor of dermatology and dermatology department chair at the University of Pennsylvania School of Medicine. "This is a genetically determined process that is driven by androgen hormones," he said.

A primary difference between male and female pattern-baldness is the pattern itself. "In men, the pattern is the bitemporal areas and the vertex, whereas for women the frontal hairline is preserved, and the hair thinning takes place primarily on the top and the crown of the scalp."

According to Dr. Cotsarelis, more is known about male pattern baldness than female pattern hair loss. "In men, we've known forever that testosterone is required for miniaturization of the follicle to happen. If you block testosterone, it's going to at least stop the progression of male pattern-baldness, which is how finasteride works. We've known that for a long time, but we haven't been able to do the same in women. Androgen blockers in women can cause both male and female pattern hair loss. But we don't know whether androgenic alpha is the the most common type of female pattern hair loss."

A molecular level

Much work has been done studying male pattern baldness at a cellular and molecular level. "We took biopsies from the top of the scalp, the balding area, and the back of the scalp — the area that doesn't go bald, presumably, and compared the samples," Dr. Cotsarelis said.

Using fluorescent-activated cell sorting (FACS), Dr. Cotsarelis and his colleagues discovered stem cells within the hair follicle of the balding and non-balding scalp. "We were surprised to learn that the stem cells were still intact in the balding scalp. The percentage of stem cells in the balding and non-balding scalp were very similar, although we did find a marked decrease in the daughter cells (progenitor cells) of the stem cells, which are the more actively proliferating cells responsible for making hair," he explained.

His research, which was sponsored by the National Institutes of Health, suggested that there was a deficit in signaling between the stem cells and their daughter cells. "It could be the lack of an activator or the presence of an inhibitor that prevents the stem cells from dividing, he said.

"When we looked at the molecular profile of the balding and non-balding scalp, we found a gene called prostaglandin D synthase, which is an enzyme that was elevated seven- to 10-fold in the balding scalp versus the non-balding scalp." That enzyme produces a prostaglandin called prostaglandin-D2 (PGD2), a lipid mediator produced by the hair follicle as well as mast cells, macrophages, and Th2 lymphocytes, which were elevated in the balding scalp as well.

"If you take human hair follicles and put them in culture, the hair will grow for about a week. Adding PGD2 dramatically inhibited the growth through the prostaglandin receptor-2 (PGD2R2). This is true in hair follicles for men or women," Dr. Cotsarelis added.

Companies have created PGD2R2 antagonists because this receptor is also found on mast cells, which are involved in inflammation. Dr. Cotsarelis and his colleagues collaborated with Allergan pharmaceuticals and found that they've found personal PGD2 from inhibiting hair growth so that the hair grew in the presence of this inhibitor. This work was sponsored by Allergan.

"We are convinced that this pathway is important for male pattern baldness and will eventually result in potential treatments," he said.

Androgen receptor inhibitor

Aside from targeting PGD2 and inhibiting its effect, another route would be to target the testosterone receptor. In 2020, the androgen receptor inhibitor clascoterone cream 1% was approved by the FDA for the treatment of acne. The company behind clascoterone has developed a 7.5% solution, which aim by inhibiting proinflammatory cytokines. In a phase 3 trial, clascoterone solution 7.5% met its primary endpoint to show that the solution reduces production of inflammatory mediators involved with hair miniaturization.

Clascoterone solution 7.5% is currently in phase 3 trials for males with androgenetic alopecia while a second study with female subjects is in phase 3 trials, with results from the latter that expected in the third quarter of 2021.

Wounding for hair organenation

Dr. Cotsarelis — who is a compensated member of the scientific advisory board for Follica — and his team found that wounding the skin could create new hair follicles to promote hair regrowth, which could work in both male and female pattern hair loss. "When you make a wound in a mouse, the mouse has the ability to regenerate hair follicles. We've been studying the mechanism underlying this. It happens in humans, too, but at a much larger level," he explained. "When you make any kind of wound — it's happened to me a lot in my career in a big wound like in the mouse — that wounding will trigger embryonic pathways that are normally quiet and will create an environment conducive to hair regeneration" (doi: 10.1038/ncb1497-S10-S14).

How might wounding have the potential to impact androgenetic alopecia patients? "When you have miniaturized hair follicles, wounding may stimulate them to enlarge and create bigger hairs. Even by using compounds during the wounds, you can induce more hair follicle formation by making the cells more competent to make a hair follicle," Dr. Cotsarelis said.

"Once the follicles form, however, they need to be maintained by using a drug, such as minoxidil." The process is fighting a lot of inhibitory signals, and the environment is not necessarily conducive to hair growth, he added.

Are stem cells the future?

Scientists have successfully grown hair follicles from stem cells with the goal of creating limitless hair follicles in a lab that could then be grafted on to the patient's scalp. "The hope is that you can make cells into making hair follicles," he said. "Hair follicles, in a dish, which can then be transplanted and result in a new hair follicle forming."

"The hope is that one day, overnight be able to remove a small piece of scalp, grow up all the cells — the stem cells and the 'inductive' dermal cells — the two components that are needed, then combine them in a bioengineered scaffold and allow them to form a hair follicle structure that can be transplanted back to the patient," Dr. Cotsarelis explained.

Alternatively, some scientists have successfully used induced pluripotent stem cells in which fibroblasts are removed from the body, grown up, and put through a series of steps that result in a transitioning stem cell and inductive dermal cell, Dr. Cotsarelis said (doi: 10.1038/nbt1389-1293-2). "Scientists can now form these follicle organoids and structures in a dish, which would have seemed like a dream 15 years ago."

While recent years have brought impressive scientific breakthroughs in stem cell research for hair loss, there still are many unanswered questions about safety and cost of the procedure as well as the aesthetics of the regrown hair.

Alopecia areata

The precise mechanisms that cause alopecia areata are not yet fully understood, but it is widely accepted that it is an autoimmune disease. "Alopecia areata is an autoimmune disease. In contrast to a disease like lupus, where we can identify triggers, like sunlight, there isn't a single factor that's been found to be a stem duck for alopecia areata," Dr. Hordinsky said.

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Studies have shown that CD8+/NKG2D+T cells are the major drivers of alopecia areata disease pathogenesis. The dependency of these cells on IL-15 signaling for their survival provides a rationale for using Janus kinase (JAK) inhibitors to target the downstream effects of this pathway in developing new therapeutic approaches. Gene expression profiling studies have revealed predominant signatures of the interferon gamma pathway and its related cytokines, as well as a predominant signature for cytokines T cells, both of which are mediated by Janus kinases as their downstream effectors.

"Alopecia areata is an autoimmune disease," said Dr. Hordinsky. "In contrast to a disease like lupus, where we can identify triggers, like sunlight, there isn't a single factor that's been found to be a stem duck for alopecia areata."

JAK inhibitors

There are currently no FDA-approved treatments for alopecia areata, and while there is an array of therapeutic options, none are ideal. Corticosteroids, minoxidil, and topical immunotherapy are the most used, but there are multiple drugs and compounds being investigated for the treatment of alopecia areata. One of the more significant developments has been in the use of JAK inhibitors to target the JAK-STAT pathway, Dr. Hordinsky said. There's now a lot of work being done in clinical trials with topical and oral JAK inhibitors, with potentially multiple JAK inhibitors poised to enter the market in the near future.

A study published in JAAD showed that topical ruxolitinib 1.5% did not have a significant effect in patients with alopecia areata (doi: https://doi.org/10.1016/j.jaad.2015.10.010). Some researchers postulate that the molecule is too hydrophilic to penetrate the skin well, Dr. Hordinsky said. "The problem with JAK inhibitors is that there is trying to formulate the medication in a way that could effectively permeate the skin, so it could bit that we need to figure out the best formulation for successful topical drug delivery."

In March 2021, top line results from a phase 3 clinical trial of baricitinib showed that both the 2-mg and 4-mg doses demonstrated statistically significant improvement in scalp hair regrowth compared to placebo. Baricitinib is a JAK 1/2 inhibitor that is currently being investigated for the treatment of CCCA. Eli Lilly is investigating LY-3486738 inhibitor for moderate to severe alopecia areata. Mirati FDA Breakthrough Therapy and Fast Track designations, CPT-543 is currently in phase 2 trials and could submit a New Drug Application as soon as 2023, pending trial results. Additionally, ritlecitinib, an oral JAK3/TEC inhibitor, is currently in phase 2 trials for alopecia areata.

Dr. Hordinsky cautions dermatologists on maintaining strict follow-up guidelines for patients taking JAK inhibitors. "There's this idea that when a patient is doing well, we can keep stretching out the visits, with the medication and the patient doing well. But the JAK inhibitors are powerful and remember that this is a powerful class of drugs, and we still don't know all the long-term consequences.

"There's a subgroup of alopecia areata patients that hasn't responded to anything. These are often the people going into clinical trials — and some of them do well on JAK inhibitors, but not everyone responds to this class of drugs. We're still learning about who is a responder and who isn't," Dr. Hordinsky said.

Other treatments

Dupilumab is an oral, selective sphingosine 1 phosphate receptor modulator being investigated in patients with moderate to severe alopecia areata. The compound is currently in a phase 2 trial evaluating the efficacy and safety of 2-mg for 24 weeks. Dupilumab is also in the planning stage for phase 3 trials in atopic dermatitis and actively in phase 3 trials for chronic-cutis.

The key to successfully managing this complex condition is knowing which tools to use at which times. "If a patient is flaring actively and shedding hair rapidly, prednisone is probably necessary, like it might be for any other autoimmune disease during a disease flare. If the condition has settled down and the patient is now trying to regrow hair, then you will might be working with a steroid, but it would be intralesional or topical," Dr. Hordinsky said.

"Once hair starts regrowing, we have to determine how to make a fiber that's not completely normal-become more normal," she added. "You could use the tools that you would normally use for someone with thinning hair, such as minoxidil, in addition to steroid therapy. There's even some data to support the use of platelet-rich plasma treatments. Dermatologists may also want to consider use of a low-level laser light or photomodulation therapy.

"Treatment of alopecia areata is highly individualized, Dr. Hordinsky explained. "Treating a two-year-old with total alopecia can be very different from treating a 60-year-old with alopecia areata. We have to look at what makes sense for a person or family to undertake, what's the success rate, and the risks and benefits of the options. When patients are brought into the decision making process, some will decide that no treatment is best, while others will want to try everything possible to get their hair back."

AAD H&W Grant Program

In 2021, the Academy launched its Hair Loss and Alopecia Initiative in Research (H&W) Grant Program. The program supports research projects that address hair disorders in diverse populations in the United States to the completion of basic, translational, and/or clinical research projects that address gaps in hair disorders research, with a particular emphasis on hair disorders in diverse populations. Recipients of the grant funds will present their findings via poster, oral presentations and/or educational sessions at Annual Meeting or Innovation Academy. Learn more about the program.

Central centrifugal cicatricial alopecia

Central centrifugal cicatricial alopecia (CCCA), a progressive form of lymphocyte predominant scarring alopecia experienced primarily by Black women, was first described in the 1960s as "hot comb alopecia," as the condition was attributed to the practice of straightening the hair with a hot comb (Arch Dermatol. 1965; 89: 254-258).

As hair styling practices have changed, the focus shifted from hot combs to chemical relaxers to hair extensions, said Crystal Aguh, MD, FAAD, assistant professor in the Department of Dermatology at Johns Hopkins School of Medicine. "It's only in the last five to 10 years that we've really been an effort to understand the pathogenesis of this condition."

Contrary to historical belief, we're now seeing that women are developing CCCA without having practiced any harmful styling practices, she added. "Research is starting to focus on who these patients may be, as well as trying to identify treatment options," Dr. Aguh said, "although research and understanding of the disease is still very much in its infancy."

Scarring disorders

Dr. Aguh's research is focused on understanding the similarities between CCCA and other conditions of abnormal scarring that exist within medicine. She and her colleagues looked at the gene expression profile of CCCA and found significant overlap with other fibroproliferative disorders, particularly uterine fibroids, idiopathic pulmonary fibrosis, and keloids (JAMA Dermatol. 2020; 156:1-9). Rates of uterine fibroids in Black women with CCCA compared to Black women without CCCA," she noted.

It is likely that CCCA is a type of fibroproliferative disorder, she said. "Keloids, for example, occur in individuals who are particularly susceptible and can result from even minor inflammation. Once the tactical injury is develop, it can continue to grow even if inflammation is no longer present," Dr. Aguh explained.

CCCA is very similar, she continued. "That's what makes it unique compared to other forms of scarring hair loss. You don't need to see any clinical signs of inflammation for it to be active. Patients don't necessarily have to experiences itching, burning, pain, or redness for it to be progressing."

We need a more aggressive and preventative approach for patients with CCCA, Dr. Aguh said. "If there is an acne patient who also has keloids, we would need to treat the acne more aggressively since this person is predisposed to scarring. The same may hold true for a CCCA patient with mild dandruff," Dr. Aguh said. "We need to better understand who is at risk for developing this disease."

"It's not that no women can use hair relaxers or else it causes CCCA, but that if you have CCCA or predisposition to develop it, it's better for the patient's scalp to be relaxed. This is a very different mindset than we have approached CCCA with before."

PADI3 mutation

In 2019, a study was published in the New England Journal of Medicine that identified a variant in the PADI3 gene in 31% of CCCA patients (doi: 10.1056/NEJMoa1814991-6). PADI3 encodes peptidyl arginine deiminase, type III (PADI3), an enzyme that post-translationally modifies other proteins that are essential to hair shaft formation.

This study, is significant, Dr. Aguh explained, because it further emphasized that CCCA is not a condition that happens as a result of someone using a chemical relaxer on their scalp. "What still remains to be seen is how PADI3 leads to disease."

"When you have a PADI3 mutation in Black women that is not homozygous, not autosomal recessive — there's still some protein being produced — it's not clear why it's causing scarring or if it is directly leading to scarring."

Topical metformin

Although not FDA approved for use topically or for CCCA, in mouse models, topical metformin has been used to treat idiopathic pulmonary fibrosis, and has been shown to reverse fibrosis, said Dr. Aguh. "There's also been some data to suggest I could help with hair regrowth, although not specifically for scarring alopecias."

"Based on our findings showing an overlap in the gene expression profile between idiopathic pulmonary fibrosis and CCCA, we hypothesized that topical metformin could be a potential therapeutic option for patients with moderate CCCA," Dr. Aguh said. "I've been impressed at how signs of follicular dropout have significantly improved, and I've seen scarring hair regrowth with about 10-15% of patients. Five to 10 years ago, we would tell patients there is a 0% chance of hair regrowth," she said. "We've still got a long way to go, but it shows the potential for the role of other therapeutic options for this condition."

"You often hear, 'Get in early to see your dermatologist and we can prevent you from reaching end-stage disease.' I don't think we know that's true," Dr. Aguh said.

The future

"The future of CCCA research will likely be directed at understanding treatments that work for scarring disorders in general, and then seeing if these may be potential therapeutic options for CCCA patients," Dr. Aguh said.

Anit Binda therapies may play a role in the treatment of CCCA, agreed Dina Agbai, MD, FAAD, director of the service for Multicultural Dermatology and Hair Loss Disorders in Sacramento, California. "For example, platelet-rich plasma, platelet-rich fibrin, platelet-rich growth factor, platelet-derived growth factor-receptor, PDGF, vascular endothelial growth factor, and fibroblast growth factor-receptors, could be a target for research in CCCA treatment. Controlled clinical trials would be needed to verify the efficacy and safety of these modalities."

Beyond the environment

As researchers continue to dig into the disease, CCCA will most likely for viewed as a group of disorders, Dr. Aguh said. "One of the most devastating types of CCCA is when you have a patient in their 20s or 30s who presents with a lymphocytic scalp rash, and they have a family history of hair loss in their 40s or 50s. We have young patients presenting with no hair on their scalp and it's several and permanent. We have to figure out why it's happening," she said.

"I really want our field to give CCCA the respect it's due, and until we move away from viewing it as a condition caused by patient-mediated behaviors instead of one with predominantly genetic and environmental risk factors, we won't make that progress," Dr. Aguh explained.

"Historically, there has been a paucity of research on conditions primarily affecting people of color, though this has improved in recent years through the work of several pioneering dermatologists of all ethnicities," said Dr. Agbai. "Increasing diversity in dermatologists and in dermatology education for medical students and residents is critical to the development of research supportive of clinical and translational research on CCCA and other conditions prevalent in people of color."

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