

News & views

Immunology

Nerve activity initiates autoimmune hair loss

Jarish N. Cohen

Understanding the triggers of autoimmunity might lead to better therapies, with hair loss among the conditions for which underpinning factors have come to light. **See p.1310**

"I'm as free as my hair," proclaims the pop star Lady Gaga in her song 'Hair'. Indeed, hair can be a statement of freedom and it informs our sense of self. Conversely, baldness (a condition called alopecia) can be considered an attack on the self, not only in a psychological sense, but also in a literal sense through autoimmunity, in which immune cells that usually ignore the body's own tissues instead damage organs and cause problems such as hair loss. On page 1310, Cui *et al.*¹ provide insights into autoimmune hair loss from their studies of mice.

The life cycle of hair and the cells that surround a hair strand involves a dance choreographed in three phases. The first is hair growth, known as anagen. Then comes regression, called catagen, in which the hair strand and surrounding tissue shrink. Finally, there is an inactive rest phase known as telogen. In humans, 80–100% of scalp hair tissue is in anagen², and if autoimmunity against hair occurs, it is during this phase³. Early work⁴ showed that skin at the anagen stage that is transplanted from one mouse strain into another is rejected faster than is a transplant using telogen-stage skin⁴, suggesting that anagen-stage skin in hair follicles is intrinsically more prone to triggering an immune response than is telogen-stage skin. Many decades later, scientists still do not have a firm grasp of why hair cells in the anagen stage of the cycle are susceptible to autoimmunity.

Anagen is initiated by hair follicle stem cells (HFSCs). These crucial cells are usually shielded from being attacked by the immune system, partly by the actions of immune cells called regulatory T cells (T_{reg}), which prevent autoimmunity⁵. Cui and colleagues observed that mice developed alopecia after the authors eliminated T_{reg} during anagen. This elimination was associated with an influx of immune cells called $CD8^+$ T cells into the skin, resulting in

autoimmune damage (Fig. 1).

Cui and colleagues investigated which cells might regulate the susceptibility to autoimmunity in this setting. By focusing on the sympathetic nervous system, the nerve cells of which are associated with HFSCs⁶, the authors discovered that expression of the protein c-FOS, which is a sign of activation of sympathetic nerves, was higher in nerve cells during anagen than during the telogen phase. The sympathetic nervous system regulates 'fight-or-flight' responses during stress and maintains unconscious bodily functions. The c-FOS finding suggested that sympathetic nerves control the autoimmune susceptibility of hair-associated tissue during anagen.

To test this hypothesis, Cui and colleagues disrupted sympathetic nerves by both surgical and chemical means following induced T_{reg} depletion during anagen. The authors found that these treatments reduced the infiltration of $CD8^+$ T cells into hair-associated skin and prevented alopecia. Moreover, either treating mice with a drug that reduces noradrenaline – a neurotransmitter molecule released by sympathetic nerve cells – or selective elimination of the noradrenaline receptor, ADRB2, on HFSCs reduced the influx of $CD8^+$ T cells into skin and diminished alopecia. These results show that noradrenaline signalling to HFSCs after sympathetic nerve activation is necessary for anagen hair to be susceptible to autoimmunity.

To find the molecules responsible for this phenomenon, the researchers adopted a technique called single-cell RNA sequencing. This method was used to survey gene-expression patterns in individual HFSCs, revealing that genes involved in antiviral responses were highly expressed when T_{reg} s were experimentally depleted. Given that viruses were not introduced during their experiments, the authors wondered whether ancient, usually dormant, virus-derived genetic material embedded in mammalian genomes, known as endogenous retroviruses (ERVs), might have become reactivated by sympathetic nerve activity during anagen, resulting in the production of viruses.

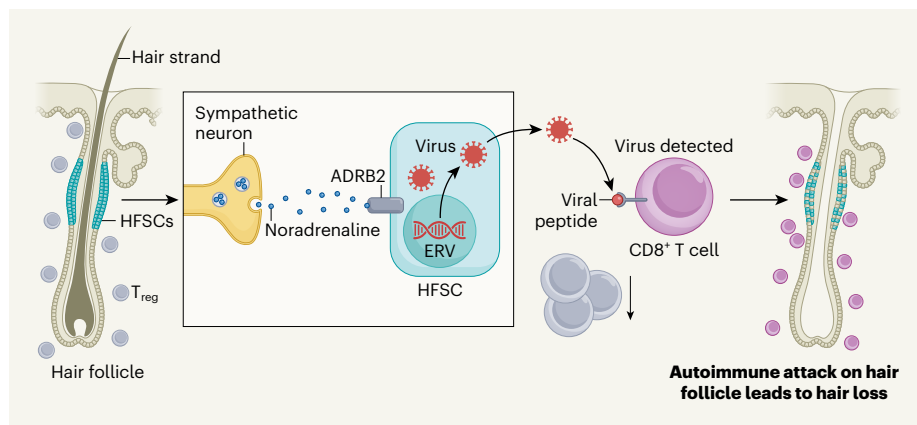


Figure 1 | How sympathetic nerve activity triggers autoimmune hair loss. Cui *et al.*¹ studied a mouse model of autoimmune hair loss, which occurs during the growth (anagen) phase of the hair cycle. A hair strand and the associated cells form a structure called the hair follicle, with hair being produced by hair follicle stem cells (HFSCs). Neurons of the sympathetic nervous system release the molecule noradrenaline, which binds to the ADRB2 receptor on HFSCs. The authors report that this signalling from the sympathetic nervous system can trigger the production of viruses from endogenous retroviral sequences (ERVs) present in the genome, which are normally dormant and do not produce viral particles. Viral peptides are recognized by immune cells called $CD8^+$ T cells, which unleash an attack on cells in the hair follicle, when immune cells called regulatory T cells (T_{reg} cells) are depleted. This autoimmune attack of hair follicles leads to a loss in production of hair strands.

Indeed, the authors found that levels of ERV viral particles increased more in anagen-stage skin than in telogen-stage skin. However, the level of the viruses was reduced by depleting sympathetic nerves or lowering the expression of ADRB2 in HFSCs. To determine whether ERV reactivation is connected to autoimmune susceptibility, the authors treated mice in anagen with antiviral drugs after T_{reg} depletion, which resulted in a diminished influx of $CD8^+$ T cells into the skin and reduced alopecia. This result indicates that ERVs are sensed and targeted by the immune system at the anagen stage.

The authors found that this autoimmunity was dependent on the protein AIM2, which is a sensor of harmful DNA. Importantly, the authors surveyed small peptide fragments of ERVs and identified one that potently activated $CD8^+$ T cells during autoimmunity. Together, the results provide a comprehensive molecular explanation for autoimmune susceptibility of anagen-stage hair in mice.

Although this discovery might have implications for the treatment of human autoimmune alopecia, several questions need to be answered first. One regards the mechanism of sympathetic nerve activation, which occurs in a precise time window during early anagen onset, according to Cui and colleagues' work. Intriguingly, different molecular cues expressed by cells neighbouring HFSCs influence the delicate balance between telogen and anagen⁷. In addition, the composition of immune cells in skin fluctuates depending on the phase of the hair cycle, which might contribute to HFSC activation as well^{8,9}. Therefore it is tempting to speculate that local factors expressed by cells in skin, such as stromal cells and immune cells, activate sympathetic nerves. Further studies should help to unlock this key piece of the puzzle.

It is unknown whether these findings will be confirmed for humans or whether the phenomenon is mouse-specific. Reactivation of ERVs has been implicated in human autoimmune disease but a precise role in causing disease has yet to be firmly established¹⁰. A study of the human autoimmune disease cutaneous lupus demonstrated expression of ERVs in a wide variety of cell types, including skin cells called keratinocytes¹¹. It will be fascinating to determine whether sympathetic nerves control ERV reactivation in human anagen-stage skin.

Although the suggestion that ERVs have a harmful role in autoimmunity is interesting, it is currently unknown how ERV viral particles are usually ignored during normal hair growth. Cui and colleagues provide a clue by showing that T_{regs} restrain ERV-specific T cells. When developing T cells encounter the body's own proteins in the immune organ called the thymus, they are either eliminated or become T_{regs} , and a similar process occurs in immune-system structures called lymph nodes during normal processes that aid immune-system function.

Interestingly, there is some evidence that ERVs are expressed in the thymus¹², suggesting that T cells capable of driving autoimmunity against hair tissue are potentially safeguarded from doing so by encountering viral proteins in this organ. Future work will be needed to uncover the precise mechanisms that normally keep ERV-specific T cells in check, and to understand how this process goes awry during autoimmunity.

Although many questions remain to be answered, Cui and colleagues' study provides a framework linking sympathetic nerve activation in anagen to ERV reactivation in HFSCs, which can initiate an autoimmune cascade in the setting of immune dysregulation. This study might pave the way for the discovery of therapeutic targets that modulate the nervous system or blunt ERV reactivation. Perhaps, by calming their nerve cells, those with autoimmune alopecia can one day reclaim a part of themselves and be as free as their hair.

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Cell biology

Glimpsing archaeal microbes on the move

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How and when did cells gain the ability to crawl? Live imaging of cells from close relatives of early eukaryotes fills in a major gap in the understanding of cellular evolution. **See p.1218**

The ability of cells to move through the environment is crucial for their survival – enabling them to seek out food or flee from danger. On page 1218, Radler *et al.*¹ shed light on how such crawling motility evolved.

Many types of eukaryotic cell (defined as having nuclei) move by crawling. This process, which depends on the protein actin, is driven by protrusions of the cell membrane, rapid ballooning out of the membrane through a process termed blebbing and intracellular movement called cytoplasmic streaming². Actin can form filaments that grow or shrink, and it can organize into filament networks that are a key component of an intracellular structure called the cytoskeleton.

The crawling movement of eukaryotic cells depends on the cells' ability to adhere to surfaces and on their dynamic cytoskeleton, which uses growing actin filaments to push membrane outwards or to pull it inwards if actin networks contract. By contrast, bacteria move through liquids using a tail-like appendage called a flagellum, or they can move on surfaces by 'twitching' – during which they tether and retract surface filaments called pili.

How did the eukaryotic crawling movement evolve? Enter the Asgard archaea, microorganisms considered to be an evolutionary link between bacteria and eukaryotes that were first identified by DNA sequencing of samples from ocean hydrothermal vents³.

The first key clues came from imaging, using cryogenic electron tomography, of the Asgard archaeon *Candidatus Lokiarchaeum ossiferum*. This work revealed that the cells contained filaments of Lokiactin, a type of actin found in Asgard archaea; genomic sequencing identified genes encoding these proteins that are closely related to eukaryotic actin⁴. The cells have a round cell body (the part of the cell that contains DNA) along with what seems to be a Lokiactin-filament network of actin proteins. They also have long, thin cellular protrusions containing parallel actin filaments, which are reminiscent of structures called eukaryotic filopodia – dynamic membrane protrusions that are supported by bundles of parallel actin filaments. These observations suggest that *L. ossiferum* has a dynamic actin cytoskeleton that might enable movement.

Radler and colleagues established a method