(Fig. 1b). When the interactions between birds are non-reciprocal, a state can emerge in which the birds fly in circles (Fig. 1c). The spatial symmetry in this state is restored because the birds fly in all directions. Importantly, this state has a chirality – the birds either all fly clockwise or all fly anticlockwise – that is stabilized by the many interactions between the birds. This stabilization prevents the system from flipping back and forth between the two chiralities, which would produce an average chirality of zero.

Fruchart *et al.* now show that the emergence of the chiral state occurs at a transition between symmetry and broken symmetry that is controlled by an exceptional point. By contrast, transitions in systems at equilibrium occur at mathematically distinct 'critical points' that are associated with the closing of an energy gap, which causes two distinct states of the system to have the same energy. The energy of a dynamic system can be described numerically by a mathematical function called a Hamiltonian, and fundamental modes of the system are characterized by vectors known as eigenvectors. The Hamiltonian of a system that has non-reciprocal interactions is non-Hermitian[1], which means that the eigenvectors are not fully independent. When the directions of these eigenvectors are varied by changing a control parameter of the system, two of the eigenvectors can coalesce at an exceptional point.

The authors show that in a many-body system, one of the two overlapping modes is known as a long-wavelength Goldstone mode, and is associated with the breaking of rotational invariance. In the case of a flock of birds, the Goldstone mode corresponds to a uniform movement of all birds along the flocking direction, whereas other modes control the relative motion of birds within the flock with respect to each other.

At the exceptional point, the complete overlap of the Goldstone mode with one of the other modes allows the system to freely switch between all possible ground states, instead of remaining trapped in one state. For the birds, this corresponds to the emergence of chiral rotation across the entire system. In other words, Fruchart *et al.* report how symmetry that was spontaneously broken on one side of the exceptional point can be dynamically restored.

Although exceptional points have received considerable attention in photonics[7], where they have been shown to describe properties such as the one-way transmission of light through a material, Fruchart and colleagues expand their use to many-body systems that are out of equilibrium. Indeed, the authors' findings apply to any system containing two key ingredients: non-reciprocal interactions and a spontaneously broken continuous symmetry. This opens up the possibility of engineering devices whose function depends on the behaviour of a non-reciprocal system that is close to its exceptional-point transition – by analogy to existing devices that exploit behaviour near ordinary phase transitions (such as a refrigerator, which repeatedly vaporizes and condenses its coolant).

For example, materials could be developed that exhibit one-way elasticity – that is, in which mechanical waves propagate undisturbed in one direction, but are totally reflected in the opposite direction. Devices could be engineered to produce coherent phonons, the mechanical equivalent of a laser beam. And it might be possible to develop mechanical strain cloaking, in which a portion of a material is fully isolated from vibrations or shocks.

Cynthia J. O. Reichhardt and **Charles Reichhardt** are in the Theoretical Division, Los Alamos National Laboratory, Los Alamos, New Mexico 87544, USA.
e-mail: cjrx@lanl.gov

1. Ivlev, A. V. *et al. Phys. Rev. X* **5**, 011035 (2015).
2. Fruchart, M., Hanai, R., Littlewood, P. B. & Vitelli, V. *Nature* **592**, 363–369 (2021).
3. Vicsek, T., Czirók, A., Ben-Jacob, E., Cohen, I. & Shochet, O. *Phys. Rev. Lett.* **75**, 1226–1229 (1995).
4. Bechinger, C. *et al. Rev. Mod. Phys.* **88**, 045006 (2016).
5. Lavergne, F. A., Wendehenne, H., Bauerle, T. & Bechinger, C. *Science* **364**, 70–74 (2019).
6. Chen, Y., Li, X., Scheibner, C., Vitelli, V. & Huang, G. Preprint at https://arxiv.org/abs/2009.07329 (2020).
7. Miri, M.-A. & Alu, A. *Science* **363**, eaar7709 (2019).

Stem cells

Relax to grow more hair

Rui Yi

A stress hormone has been found to signal through skin cells to repress the activation of hair-follicle stem cells in mice. When this signalling is blocked, hair growth is stimulated. Stressed humans, watch out. **See p.428**

When American football quarterback Aaron Rodgers told his fans to relax after his team's poor start one season, little did he know that he was also giving a hair-care tip. His advice is particularly helpful now, after a long pandemic year. About one-quarter of people who contract COVID-19 experience hair loss six months after the onset of symptoms[1], probably because of the systemic shock caused by the ordeal of infection and recovery. Chronic stress has long been associated with hair loss, but the underlying mechanism that links stress to the dysfunction of hair-follicle stem cells has been elusive. On page 428, Choi *et al.*[2] uncover the connection in mice.

Throughout a person's lifespan, hair growth cycles through three stages: growth (anagen), degeneration (catagen) and rest (telogen). During anagen, a hair follicle continuously pushes out a growing hair shaft. During catagen, hair growth stops and the lower portion of the hair follicle shrinks, but the hair (now known as a club hair) remains in place. During telogen, the club hair remains dormant for some time, eventually falling out. Under severe stress, many hair follicles enter telogen prematurely and the hair quickly falls out.

Hair-follicle stem cells (HFSCs) are located in a region of the hair follicle called the bulge. These cells have a crucial role in governing hair growth by interpreting both internal and external signals. For example, during telogen, HFSCs are kept in a quiescent state and so do not divide[3,4]. When hair growth is initiated in the next anagen phase, HFSCs are instructed to divide and produce progenitor cells. These progenitors then begin a journey of differentiation, generating several layers of hair follicles and, ultimately, the hair shaft.

Since HFSCs were identified in the bulge region more than 30 years ago[5–7], many regulatory molecules – such as gene-transcription factors and signalling proteins – have been shown to control the cells' quiescence and activation[3,4]. Nearly all of these regulators are produced by either HFSCs or their neighbouring cells, including dermal papilla cells, which usually function as a supportive 'niche' for HFSCs[8,9]. But how systemic conditions such as chronic stress affect the activity of HFSCs is incompletely understood.

To answer this question, Choi and colleagues first tested the role of adrenal glands – which produce stress hormones and constitute a key endocrine organ – in the regulation of hair growth, by surgically removing them from mice. Telogen phases were much shorter in the hair follicles of these animals (which the team dubbed ADX mice) than in control mice (less than 20 days compared with 60–100 days), and the follicles engaged in hair growth roughly three times as often. The authors were able to suppress this frequent hair growth and restore the normal hair cycle

by feeding the ADX mice corticosterone (a stress hormone normally produced by the animals' adrenal glands). Interestingly, when they unpredictably applied various mild stressors to normal mice for nine weeks, they observed elevated corticosterone levels accompanied by reduced hair growth, supporting the idea that corticosterone produced by the adrenal glands during chronic stress inhibits the initiation of hair growth.

How do HFSCs sense corticosterone? Because corticosterone signals through a protein known as the glucocorticoid receptor, selective deletion of this receptor in different cell types in the skin should reveal which cells are required to receive the signal. Choi *et al.* found that selective deletion in the dermal papillae blocked the inhibitory effects of corticosterone on hair growth, whereas deletion in HFSCs themselves had no effect. This suggests that HFSCs do not sense the stress hormone directly – and that, instead, the dermal papillae have a crucial role in signal transmission.

To understand how dermal papillae relay the stress signal onwards to HFSCs, the authors profiled the messenger RNAs (which serve as the template for protein production) that are expressed in dermal papillae. This pointed to a secreted protein called growth arrest-specific 6 (GAS6) as a candidate molecular messenger. Indeed, delivering GAS6 into the skin using an adenovirus vector (a common tool in gene therapy) not only stimulated hair growth in normal mice, but also restored hair growth during chronic stress or corticosterone feeding.

Next, Choi and colleagues found that the protein AXL – a receptor for GAS6 that is expressed by HFSCs – passes the signal on to HFSCs to stimulate cell division. These and other data generated by the authors show that corticosterone signalling, triggered by chronic stress, leads to inhibition of GAS6 production in dermal papillae, and that forced expression of GAS6 in the dermis can bypass the inhibitory effect of chronic stress on hair growth (Fig. 1).

These exciting findings establish a foundation for exploring treatments for hair loss caused by chronic stress. Before this knowledge can be applied to humans, however, several issues should be carefully examined. First, although corticosterone is considered to be the rodent equivalent of human cortisol, we do not yet know whether cortisol signals in a similar fashion in humans. Characterization of GAS6 expression in human dermal papillae during the hair-growth cycle, and under stressed conditions, will be one of the first steps to take.

Second, the duration of hair-cycle phases is different in mice and humans. In adult mice, most hair follicles are in the telogen phase at any given time, compared with only around 10% of human hair follicles[10]. This point is particularly important because, in inhibiting GAS6 production, Choi *et al.* showed that corticosterone had a role in prolonging telogen. They did not comprehensively evaluate the anagen phase, which accounts for the status of roughly 90% of follicles in the human scalp. It will be interesting to see whether chronic stress, and perhaps cortisol, can 'push' anagen hair follicles into telogen in humans, or whether these factors serve only to prolong telogen, as in mice.

Third, although hair shedding in response to severe stress usually occurs during telogen, it is not well understood how a prolonged telogen contributes to the reduced anchorage of hair follicles, eventually leading to hair loss. In both mice and humans, the loss of telogen hair follicles through hair plucking usually stimulates a new round of hair growth. So perhaps hair loss that is induced by chronic stress is promoted by mechanisms that both reduce the anchorage of follicles and inhibit entry to the anagen phase.

Finally, Choi *et al.* have shown that GAS6 promotes the expression of several genes involved in cell division in HFSCs, without interfering with known transcription factors and signalling pathways. So, the authors might have uncovered a previously unknown mechanism that stimulates HFSC activation directly by promoting cell division. In ageing skin, most progenitor cells harbour DNA mutations – including harmful ones that are often found in skin cancers – without forming tumours[11]. It will be crucial to see whether forced GAS6 expression could inadvertently unleash the growth potential of these quiescent but potentially mutation-containing HFSCs.

Although further studies are needed, Choi *et al.* have beautifully uncovered a cellular and molecular mechanism that links stress hormones produced by adrenal glands to the activation of HFSCs through the control of GAS6 expression in dermal papillae. Moreover, they have shown that injecting GAS6 into the skin can reinitiate hair growth in mice even when the animals are experiencing chronic stress. Modern life for humans is inevitably stressful. But perhaps, one day, it will prove possible to combat the negative impact of chronic stress on our hair, at least – by adding some GAS6.

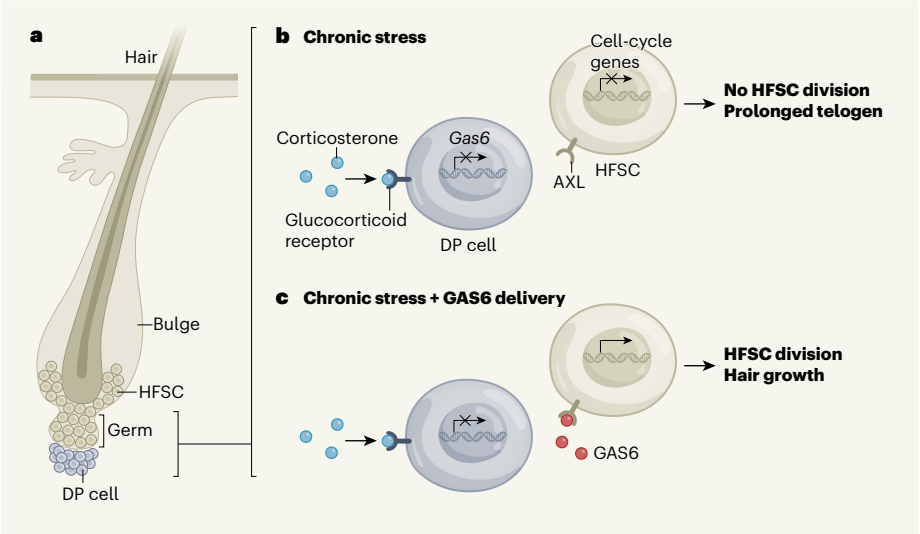

Figure 1 | Stress and hair growth in mice. a, Hair is generated from hair-follicle stem cells (HFSCs), which are thought to reside in the bulge and germ region of hair follicles during a 'resting' phase of hair growth called telogen. HFSCs are supported by neighbouring dermal papilla (DP) cells. Choi *et al.*[2] have discovered a pathway in mice that modulates hair growth in response to stress. **b**, Chronic stress causes mice to produce the hormone corticosterone. The authors show that corticosterone binds to the glucocorticoid receptor protein on DP cells, which leads to a block in expression of the *Gas6* gene. GAS6 protein would normally activate the AXL receptor protein on HFSCs. Its absence means that no activation signal is passed to the HFSCs, and no genes associated with the cell cycle are activated. The telogen phase is prolonged, and so the hair does not grow. **c**, When GAS6 is delivered into the skin using a viral vector (vector not shown), it can bind to AXL on HFSCs, triggering expression of genes involved in cell division. The HFSCs multiply, and hair growth follows.

Rui Yi is in the Department of Pathology and the Department of Dermatology, Northwestern University Feinberg School of Medicine, Chicago, Illinois 60611, USA.
e-mail: yir@northwestern.edu

1. Huang, C. *et al. Lancet* **397**, 220–232 (2021).
2. Choi, S. *et al. Nature* **592**, 428–432 (2021).
3. Blanpain, C. & Fuchs, E. *Science* **344**, 1242281 (2014).
4. Yi, R. *Stem Cells* **35**, 2323–2330 (2017).
5. Cotsarelis, G., Sun, T.-T. & Lavker, R. M. *Cell* **61**, 1329–1337 (1990).
6. Tumbar, T. *et al. Science* **303**, 359–363 (2004).
7. Morris, R. J. *et al. Nature Biotechnol.* **22**, 411–417 (2004).
8. Driskell, R. R., Clavel, C., Rendl, M. & Watt, F. M. *J. Cell Sci.* **124**, 1179–1182 (2011).
9. Hsu, Y.-C., Li, L. & Fuchs, E. *Nature Med.* **20**, 847–856 (2014).
10. Oh, J. W. *et al. J. Invest. Dermatol.* **136**, 34–44 (2016).
11. Murai, K. *et al. Cell Stem Cell* **23**, 687–699 (2018).

This article was published online on 31 March 2021.