News & views

Stem cells

Fight or flight turns hair white

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Signalling from the sympathetic nervous system of mice when subjected to stress leads to the depletion of a stem-cell population in their hair follicles. This discovery sheds light on why stress turns hair prematurely grey. **See p.676**

It has been said that Marie Antoinette's hair went completely white on the night before her beheading. This story might be apocryphal, but rapid greying of the hair is now widely referred to as Marie Antoinette syndrome. It is often assumed to be caused by stress – a phenomenon perhaps best exemplified by photographs of heads of state before and after they held office. However, the relative contributions of ageing, genetic factors and stress to greying are not known – in part owing to a lack of mechanistic understanding of the process. On page 676, Zhang *et al.*[1] identify the mechanism governing premature greying in mice that have experienced stress.

The average human scalp has 100,000 hair follicles, and a wide range of hair colours can be found across the human population. Hair colour is determined by cells called melanocytes, which produce different combinations of light-absorbing melanin pigments[2]. Melanocytes are derived from melanocyte stem cells (MeSCs), which are located in a part of the hair follicle called the bulge[3]. The normal hair cycle is divided into three stages: hair-follicle regeneration (anagen), degeneration (catagen) and rest (telogen). Melanocyte production begins early in the anagen phase (Fig. 1a). As people age, the pool of MeSCs is gradually depleted – and so pigmented hair becomes 'salt and pepper' coloured, and then turns to grey and finally to white after a complete loss of pigment in all hair follicles[4].

Aside from ageing, there are several factors that bring about premature greying, including dietary deficiencies[5], disorders such as alopecia areata or vitiligo[6,7], and stress[8,9]. Zhang *et al.* set out to test the role of stress in the greying process in mice. They exposed the animals to three different stressors – pain, restraint and a model of psychological stress – during different phases of hair growth. Each stressor caused depletion of MeSCs from the bulge region, eventually leading to the development of patches of white hair.

Prevailing theories posit that stress-induced greying involves hormones (such as corticosterone) or autoimmune reactions[10]. Zhang and colleagues examined these potential mechanisms, first by preventing corticosterone signalling and next by stressing animals that had compromised immune systems. In both cases, greying occurred after stress, indicating that neither corticosterone nor autoimmune reactions cause MeSC depletion. However, the authors found that MeSCs express β_2-adrenergic receptors, which respond to noradrenaline – a neurotransmitter molecule involved in the 'fight or flight' response to stress. Loss of this receptor specifically in MeSCs completely blocked stress-induced greying.

Adrenal glands are the main source of circulating noradrenaline. But, surprisingly, the researchers discovered that removing these glands did not prevent greying in response to stress in the mice.

Another source of noradrenaline is the sympathetic nervous system (SNS), which is highly active in response to stress, and which drives the fight-or-flight response. Zhang and colleagues showed that bulge regions are highly innervated by sympathetic neurons, and that ablating the SNS using a neurotoxin molecule, or blocking the release of noradrenaline from sympathetic neurons, prevented stress-induced greying. Next, the authors

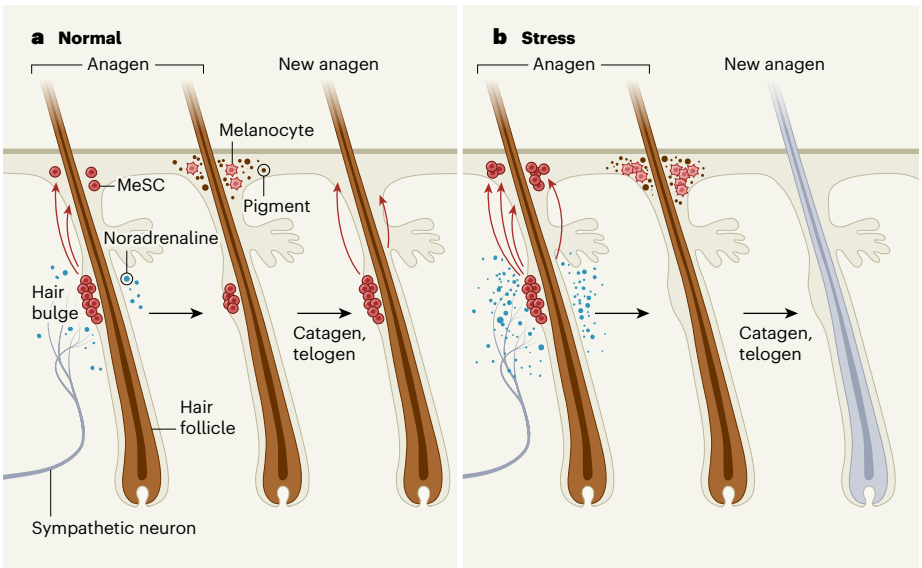

Figure 1 | Melanocyte stem cells and stress. Melanocyte stem cells (MeSCs) are located in the bulge of the hair follicle, which is innervated by neurons of the sympathetic nervous system that release the neurotransmitter molecule noradrenaline. The follicle cycles through three phases: regeneration (anagen), degeneration (catagen) and rest (telogen). **a**, Under normal conditions, MeSCs migrate away from the bulge (red arrows) and differentiate into melanocytes during anagen. Melanocytes synthesize pigments that add colour to the regenerating hair. During catagen and telogen, they begin to die and migrate out of the niche (not shown). However, plentiful MeSCs remain to replace the melanocytes in the next anagen phase. **b**, Zhang *et al.*[1] show that stressful stimuli activate the sympathetic nervous system, increasing noradrenaline release in hair follicles. Noradrenaline causes complete conversion of MeSCs into melanocytes, which migrate out of the niche in catagen and telogen. The hair follicle is depleted of MeSCs that would have differentiated to replace these melanocytes. Without any pigment cells to colour the hair in the next anagen phase, it begins to look grey or white.

generated mice in which sympathetic neurons could be acutely activated, and found that overactivation of the SNS in these mice caused greying in the absence of stress. Together, these results indicate that noradrenaline released from active sympathetic neurons triggers MeSC depletion (Fig. 1b). Interestingly, Zhang *et al.* found that the propensity of an area to turn grey correlates with its level of sympathetic innervation.

Exactly how does sympathetic activity cause depletion of MeSCs from hair follicles? Normally, these stem cells are maintained in a dormant state until hair regrowth is required. However, when the researchers tracked MeSCs labelled with a fluorescent protein, they discovered that MeSC proliferation and differentiation increase markedly under extreme stress or exposure to a high level of noradrenaline. This results in mass migration of melanocytes away from the bulge, and leaves no remaining stem cells. To further confirm this result, the researchers suppressed MeSC proliferation pharmacologically and genetically. When proliferation was dampened, the effects of stress on MeSC proliferation, differentiation and migration were blocked.

Zhang and colleagues' work raises several questions. For instance, is the mechanism underlying MeSC depletion in response to stress the same as that which causes greying during ageing? Future experiments modulating SNS activity over a longer period would determine whether age-related greying can be slowed or hastened. Perhaps, in the absence of sympathetic signals, MeSCs have the capacity for unlimited replenishment, pointing to a way to delay age-related greying.

Are other pools of stem cells similarly susceptible to stem-cell depletion in response to stress, if they or the cells that make up their niche express β_2-adrenergic receptors? In support of this idea, haematopoietic stem and progenitor cells (HSPCs), which give rise to blood and immune lineages, reside in a bone-marrow niche that contains stromal cells, and stimulation of those cells by the SNS causes HSPCs to leave their niche[11,12]. Perhaps, like MeSCs, stress depletes HSPCs — which could partially explain why immune function is impaired in response to chronic stress[13,14]. Whether this type of relationship extends beyond MeSCs and HSPCs is an open question.

It is fascinating to consider what possible evolutionary advantage might be conferred by stress-induced greying. Because grey hair is most often linked to age, it could be associated with experience, leadership and trust[15]. For example, adult male silverback mountain gorillas (*Gorilla beringei beringei*), which get grey hair on their backs after reaching full maturity, can go on to lead a gorilla troop[16]. Perhaps an animal that has endured enough stress to 'earn' grey hair has a higher place in the social order than would ordinarily be conferred by that individual's age.

Connecting the dots between stress, fight or flight, stem-cell depletion and premature greying opens up several avenues for future research. Beyond developing anti-greying therapies, Zhang and colleagues' work promises to usher in a better understanding of how stress influences other stem-cell pools and their niches.

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Cardiovascular biology

Suspect that modulates the heartbeat is ensnared

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The activity of calcium channels in the heart increases during what is called the fight-or-flight response. An investigation into the 50-year-old mystery of how this occurs has captured a previously overlooked suspect. **See p.695**

In the Sherlock Holmes tale *The Adventure of the Dancing Men*, the detective runs a heart-pounding race to try to save his client's life. The thumping of the sleuth's heart — a literary example of the 'fight-or-flight' effect[1] — reflects the changes that occur when the entry of calcium ions into the heart rises[2]. On page 695, Liu *et al.*[3] provide a solution to the long-standing riddle of how this occurs, through deductions worthy of Sherlock Holmes.

Some aspects of how calcium enters the heart during a fight-or-flight response are known. The process is mediated by the hormone adrenaline acting on β-adrenergic receptors — proteins that reside in the surface membrane of heart cells called cardiomyocytes. Receptor activation leads to an increase in the opening of what is called an L-type voltage-gated calcium channel. This occurs through a mechanism that involves the molecule cyclic AMP (cAMP)[4,5] and an enzyme called protein kinase A (PKA) that requires cAMP for its function[6]. Similar types of PKA-mediated processes are found in other contexts. For example, some neurons use cAMP and PKA to enhance calcium entry through L-type calcium channels[7].

Exactly how the stimulation of β-adrenergic receptors modulates calcium-ion influx has been debated since the 1970s. Researchers have uncovered tantalizing clues to the identity of the target molecule that PKA modifies by the addition of a phosphate group (phosphorylation). However, proposals for specific candidate targets, phosphorylation sites[8–10] and modulatory mechanisms have been repeatedly called into question by further tests, including some in painstakingly constructed mouse models[11–13]. Liu *et al.* use a powerful technique called proximity proteomics[14] to implicate a previously under-appreciated suspect[15] and to establish its role.

L-type voltage-gated channels provide a route by which calcium ions enter cardiomyocytes to help trigger a heartbeat. If channel opening is boosted, this results in a stronger and faster heartbeat. Previous investigations of how PKA might modulate channel opening focused mainly on amino-acid residues in the channel that occur in structural motifs possibly phosphorylated by PKA. But when Liu and colleagues performed a tour-de-force experiment in mice in which the channel was engineered so that all candidate