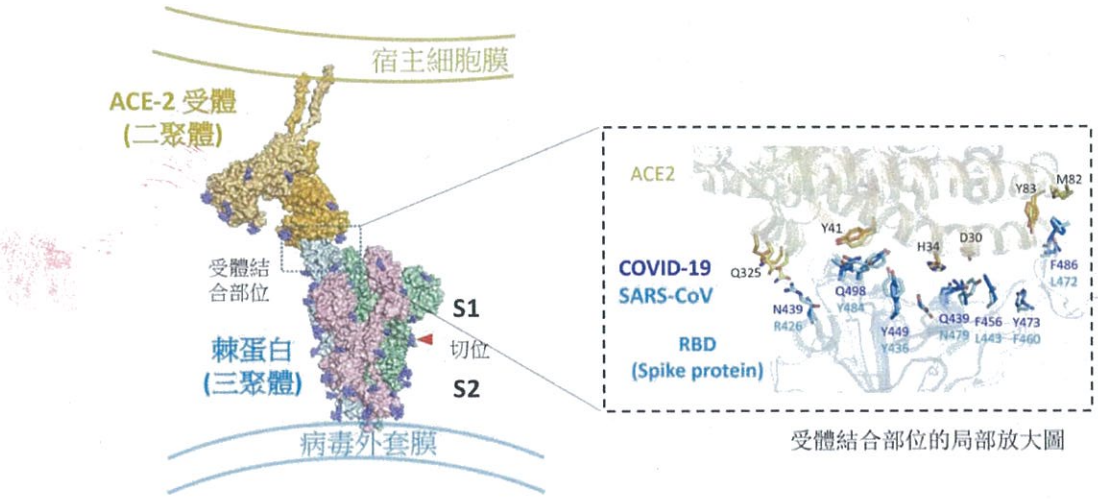
人類的新危機：新型冠狀病毒

新型病毒出現

2019 年 11 月，中國湖北省武漢市一張胸部電腦斷層掃描宣告出現新型肺炎案例，隨著人潮流動，逐漸發生了新型肺炎的人傳人感染，而且快速的蔓延到全球。科學界了解這是一種新型的 RNA 冠狀病毒（被稱為 COVID-19，新型冠狀病毒），但人們低估了其影響力，疫情迅速從中國傳到歐洲地區、美洲地區，全世界的死亡和感染病例以指數型曲線與日俱增。第一個新型冠狀病毒基因體序列在 2019 年底解碼，各地也陸續完成各株病毒基因體序列，目前在超過 2000 多筆的基因體序列上發現證實這些病毒源自相同來源，但也持續變異。透過基因序列比較，COVID-19 與 2003 年出現的嚴重急性呼吸症候群冠狀病毒 SARS-CoV 的基因相同度約有 80%，但是與雲南採集到的一株菊頭蝠冠狀病毒 RaTG13，整體基因相同度高達到 96%。

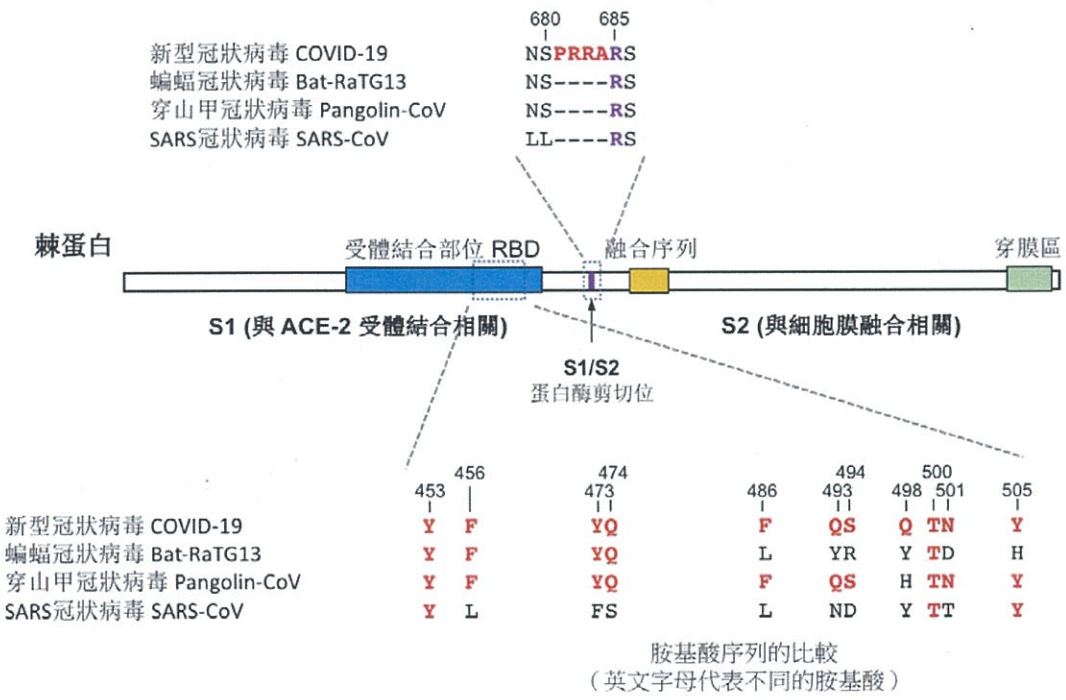
冠狀病毒的棘蛋白

冠狀病毒表面的棘蛋白（Spike protein），在電子顯微鏡下看起來就像是皇冠周圍的凸起裝飾，而冠狀病毒染細胞的關鍵就是利用病毒表面的棘蛋白，透過與人體細胞膜上的 ACE-2 受體結合後進入細胞。棘蛋白是三聚體結構，而 ACE-2 受體位於細胞表面，為二聚體結構。棘蛋白包含 S1 及 S2 兩個結構區域（structural domain）：S1 具有受體結合部位（receptor-binding domain, RBD），與 ACE-2 結合有關；S2 具有融合胜肽序列，負責與細胞膜融合；S1 及 S2 中間帶有一處可被細胞表面蛋白酶 Furin 剪切的序列，細胞中廣泛含有的 Furin，切開 S1 與 S2 後，棘蛋白一分為二，其中融合序列暴露後，開啟融合細胞的步驟，進而感染細胞，而剪切的序列中必需包含帶正電的精胺酸（胺基酸代號為 R），精胺酸的數目越高，會讓 Furin 剪切的效率變好。



受體結合部位的局部放大圖

當我們想了解新型冠狀病毒為何有如此強的感染力，就必須先分析棘蛋白及 ACE-2 受體的胺基酸序列。然而，單比較新型冠狀病毒與 SARS-CoV 的棘蛋白基因，約只有 75% 的相同度，仔細比較後，有二處值得注意的差異。第一個不同之處是在棘蛋白的受體結合部位（RBD）會與 ACE-2 形成緊密的複合體，結合介面的氨基酸種類扮演絕對的角色，但在結合位置的十一個關鍵氨基酸，COVID-19 及 SARS-CoV 兩株病毒差異達到了八個胺基酸，藉由氨基酸的不同，COVID-19 與 ACE-2 受體的結合常數，較 SARS-CoV 提高了 20 倍。另一個特別之處，是在 S1 及 S2 中間多了一小段四個氨基酸的蛋白質序列 PRRA，加上原本的胺基酸序列中的精胺酸（R），短短的五個胺基酸中就帶有三個精氨酸。



未定的演化過程

過去 SARS-CoV 被認為來自果子狸身上的一株病毒，所以果子狸被視為 SARS-CoV 的中間宿主。雖然整體上，COVID-19 基因體序列與 RaTG13 已經相當接近，單就棘蛋白基因部分也是極為相似，相同度有 93%。但在棘蛋白的受體結合部位的關鍵胺基酸，兩株病毒卻仍存在差異，所以，是否人跟蝙蝠中間是否還有其他中間宿主呢？目前有一些有趣的發現：科學家在廣東野生動物救護中心收集到的穿山甲樣品上找到一株冠狀病毒，但棘蛋白的受體結合部位（RBD）與新型冠狀病毒幾乎使用相同的氨基酸，相當獨特。此外，PRRA 序列成為尋找新型冠狀病毒演化足跡的重要片段，但目前所有已知的野生株冠狀病毒都沒有這段序列，宛如天外飛來一筆的加入新型冠狀病毒的棘蛋白基因中。最後，新型冠狀病毒的棘蛋白除了與人類 ACE-2 有高度專一的結合性，在實驗中，也可以感染帶有蝙蝠、果子狸、鳥類等不同生物 ACE-2 受體的細胞，而蝙蝠、果子狸、鳥類，甚至蛇都帶有與人類 ACE-2 相當類似 ACE-2 受體。

因為冠狀病毒是一種人與動物可能共通的病毒，野生動物及人類高密度聚集的交易場所（華南海鮮市場）是否有可能提供了大自然從沒預想過的場景，發生不可思議的跨物種交叉感染，成為基因重組、累積突變的溫床？當然，這樣的結果會不會也可能來自人類與不同野生動物交叉傳染後，基因不斷重組、累積突變成具有超強感染力的新型冠狀病毒，再次回到人類跟人類間的傳染，最後爆發出疫情。

單選題：

1：對新型冠狀病毒的以下描述，有哪些是正確的？

(a) 棘蛋白及 ACE-2 受體都是病毒的膜蛋白。
(b) 棘蛋白只要有 S2 結構區域時，就能感染細胞。
(c) 棘蛋白及 ACE-2 結合力強弱取決於 S1 結構區域的受體結合部位（RBD）的胺基酸種類
(d) 推測棘蛋白及 ACE-2 結合力，可能是 COVID-19 > SARS-CoV > RaTG13 > 穿山甲-CoV
(e) 棘蛋白及 ACE-2 結合後，ACE-2 會被融入新型冠狀病毒外套膜中

2：對新型冠狀病毒的起源，以下描述哪一個符合現有的證據？

(a) 根據棘蛋白受體結合部位的胺基酸變異，穿山甲可能是另一個中間宿主。
(b) 目前所有已知的野生株冠狀病毒都沒有 PRRA 序列，證實新型冠狀病毒是人工製造。
(c) 低等生物會將病毒傳播給高等生物，人類的新型冠狀病毒是最進化的，不會再傳染給其他動物。
(d) 即使基因序列並不是最相近，但因為臨床症狀相似， COVID-19 與 SARS-CoV 仍是同一株病毒。
(e) 新型冠狀病毒的起源可能是在華南海鮮市場吃到不乾淨的蝙蝠或是穿山甲所造成。

3：與 SARS-CoV 相比，COVID-19 似乎對人類傳染力更加強大，以下哪些五個選項中，哪兩個可能是 COVID-19 有更強的傳染力的原因？

(1) 因為蝙蝠跟果子狸相比，與人類的親緣關係更為接近。
(2) 針對 S1 及 S2 間的 PRRA 序列，Furin 可能帶來更高效率的蛋白質剪切，可增加細胞膜融合效率。
(3) COVID-19 是 SARS-CoV 演化後的病毒，長期與人類共存後，突變增強了傳染力。
(4) COVID-19 的棘蛋白受體結合部位與 ACE-2 結合力更強，專注性更高。
(5) 棘蛋白是 COVID-19 及 RaTG13 特有的蛋白質，SARS-CoV 並沒有棘蛋白。

(a) 1, 2
(b) 2, 3
(c) 3, 4
(d) 4, 5
(e) 2, 4

4：人類新冠病毒可能一開始潛伏在中間宿主中，進而感染人類，所以推斷出新型冠狀病毒演化的真正來源，找到中間宿主帶有相同的冠狀病毒是相當重要的，以下五個描述，哪一個不該是冠狀病毒中間宿主的特性？

(a) 中間宿主的數量要足夠，最好有群聚生活來交互傳染。
(b) 病毒對中間宿主必須有極強的致病性，可以導致死亡，才有可能在感染人類後成為重大疾病。
(c) 中間宿主必須與人類的生活有交集的機會，才能感染人類。
(d) 中間宿主需帶有 ACE-2 基因，才能在中間宿主及人類間交互感染。
(e) 病毒從中間宿主傳染到人類後，還會有再突變的機會。

5：下述是我們想對新型冠狀病毒的棘蛋白發展出的臨床檢驗或是治療方法，以下哪一個方法是不可行的？

(a) 利用反轉錄聚合酶連鎖反應（RT- PCR）來對檢體作多次反應，放大棘蛋白的 RNA 基因序列，驗證是否感染。
(b) 生產針對棘蛋白的單株抗體，注射到體內，達到中和 COVID-19 病毒的效果
(c) 針對裁切相關的人體蛋白酶 Furin 設計出抑制藥物來抑制棘蛋白裁切、減緩感染。
(d) 由帶原 RaTG13 冠狀病毒的菊頭蝠血液中取得血清，用來中和 COVID-19 病毒，達到治癒的效果。
(e) 利用將棘蛋白放置於快篩晶片的表面，偵測血液中是否有 COVID-19 抗體的存在，區分是否曾被新型冠狀病毒感染。

The New York Times | https://nyti.ms/2RHbc5C

TRILOBITES

Stress Really Does Make Hair Go Gray Faster

The same nerves involved in the fight-or-flight response can cause permanent damage to the cells responsible for producing hair color in mice, scientists have found.

By Knvul Sheikh

Jan. 22, 2020

There is some truth to the longstanding anecdote that your locks can lose color when you're stressed.

A team of researchers has found that in mice, stressful events damage the stem cells that are responsible for producing pigment in hair. These stem cells, found near the base of each hair follicle, differentiate to form more specialized cells called melanocytes, which generate the brown, black, red and yellow hues in hair and skin. Stress makes the stem cells differentiate faster, exhausting their number and resulting in strands that are more likely to be transparent — gray.

The study, published Wednesday in Nature, also found that the sympathetic nervous system, which prepares the body to respond to threats, plays an important role in the graying process.

"Normally, the sympathetic nervous system is an emergency system for fight or flight, and it is supposed to be very beneficial or, at the very least, its effects are supposed to be transient and reversible," said Ya-Chieh Hsu, a stem cell biologist at Harvard University who led the study.

The sympathetic nervous system helps mobilize many biological responses, including increasing the flow of blood to muscles and sharpening mental focus. But the researchers found that in some cases the same system of nerves permanently depleted the stem cell population in hair follicles.

The findings provide the first scientific link between stress and hair graying, Dr. Hsu said.

Stress affects the whole body, so the researchers had to do some sleuthing to figure out which physiological system was conveying its effects to hair follicles.

At first, the team hypothesized that stress might cause an immune attack on melanocyte stem cells. They exposed mice to acute stress by injecting the animals with an analogue of capsaicin, the chemical in chili peppers that causes irritation. But even mice that lacked immune cells ended up with gray hair.

Next, the scientists looked at the effects of the stress hormone cortisol. Mice that had their adrenal glands removed so they couldn't produce cortisol still had hair that turned gray under stress.

The system responsible for the appearance of silvery strands turns out to be the sympathetic nerves that branch out into each hair follicle in the skin.

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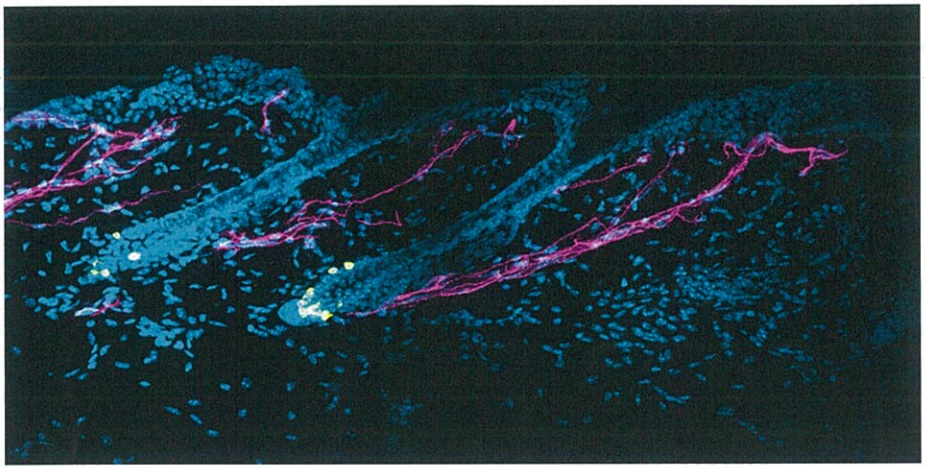

A microscope image shows the sympathetic nerves (magenta) surrounding melanocyte stem cells (yellow). Bing Zhang and Ya-Chieh Hsu

The researchers found that the sympathetic nerve cells released a neurotransmitter called noradrenaline that was taken up by nearby melanocyte stem cells. Then a series of events unfolded in quick succession: The melanocyte stem cells proliferated and turned into specialized pigment-producing cells, which abandoned their niche near the base of the follicle and left the hair without a source of pigmentation.

In Dr. Hsu's study, acute stress depleted the entire melanocyte stem cell population in mice in just five days. The researchers also found that, in petri dishes, noradrenaline prompted human melanocyte stem cells to proliferate, suggesting that the same acceleration of hair graying occurs in people, too.

"I was amazed by how dramatic this change is," said Mayumi Ito, a biologist at the New York University School of Medicine who was not involved in the study. In her own research on aging mice, the graying process was gradual: The depletion of melanocyte stem cells led first to a few salt and pepper strands and then to gray or white fur, much as humans begin to see more white hair as they get older.

Dr. Hsu's team also found that the graying process in mice could be halted with drugs known as CDK inhibitors, which stop the proliferation of stem cells, or by blocking the release of noradrenaline.

The findings underscore the consequences of triggering a survival mechanism when the situation isn't life-threatening.

"Stress is a normal part of life, but there are situations where stress is helpful and situations where it is detrimental," said Subroto Chatterjee, a biologist at Johns Hopkins University who studies the effects of stress on the cells in blood vessels.

Other studies have shown that stress is just one factor affecting how quickly hair goes gray, Dr. Chatterjee said. Genes and diet play a big role as well.

In a 2018 study, Dr. Chatterjee and his colleagues found that mice placed on the equivalent of a Western diet — high in fat and cholesterol — not only developed inflamed arteries, they also started going gray and experiencing hair loss. (The team also found a way to halt the process.)

But the new study is an important step toward understanding the role of stress on various tissues.

"If we can know more about how our tissues and stem cells change under stress, we can eventually create treatments that can halt or reverse its detrimental impact," Dr. Hsu said.

Correction: Jan. 23, 2020

Because of an editing error, an earlier version of this article misidentified the research team that found that graying in mice could be halted with CDK inhibitors or by blocking the release of noradrenaline. It was Ya-Chieh Hsu's team, not Mayumi Ito's team.

A version of this article appears in print on Jan. 28, 2020, Section D, Page 2 of the New York edition with the headline: Imperiled Pigments: How Stress Makes Your Hair Go Gray

Article

Hyperactivation of sympathetic nerves drives depletion of melanocyte stem cells

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Bing Zhang[1], Sai Ma[1,2,3], Inbal Rachmin[4], Megan He[1,5], Pankaj Baral[6], Sekyu Choi[1], William A. Gonçalves[7], Yulia Shwartz[1], Eva M. Fast[1,8], Yiqun Su[4], Leonard I. Zon[1,8,9], Aviv Regev[2,3,9], Jason D. Buenrostro[1], Thiago M. Cunha[6,10], Isaac M. Chiu[6], David E. Fisher[4] & Ya-Chieh Hsu[1]*

Empirical and anecdotal evidence has associated stress with accelerated hair greying (formation of unpigmented hairs)[1,2], but so far there has been little scientific validation of this link. Here we report that, in mice, acute stress leads to hair greying through the fast depletion of melanocyte stem cells. Using a combination of adrenalectomy, denervation, chemogenetics[3,4], cell ablation and knockout of the adrenergic receptor specifically in melanocyte stem cells, we find that the stress-induced loss of melanocyte stem cells is independent of immune attack or adrenal stress hormones. Instead, hair greying results from activation of the sympathetic nerves that innervate the melanocyte stem-cell niche. Under conditions of stress, the activation of these sympathetic nerves leads to burst release of the neurotransmitter noradrenaline (also known as norepinephrine). This causes quiescent melanocyte stem cells to proliferate rapidly, and is followed by their differentiation, migration and permanent depletion from the niche. Transient suppression of the proliferation of melanocyte stem cells prevents stress-induced hair greying. Our study demonstrates that neuronal activity that is induced by acute stress can drive a rapid and permanent loss of somatic stem cells, and illustrates an example in which the maintenance of somatic stem cells is directly influenced by the overall physiological state of the organism.

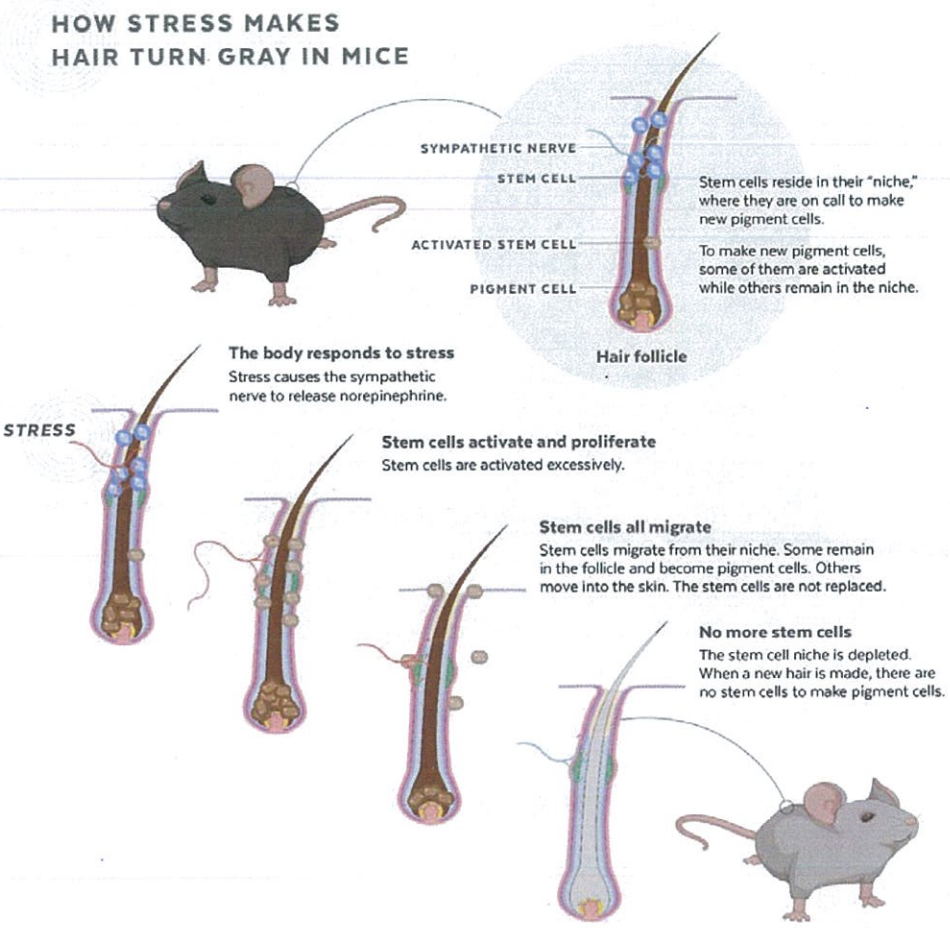
Stress has been anecdotally associated with a variety of changes in tissues, including hair greying. However, whether external stressors are the causal factors, and whether stress-related changes occur at the level of somatic stem cells, remain poorly understood. The hair follicle cycles between growth (anagen), degeneration (catagen) and rest (telogen)[5]. The bulge and hair germ region of the follicle contains two populations of stem cells: hair follicle stem cells (HFSCs), which are epithelial tissues, and melanocyte stem cells (MeSCs)[6], which are derived from the neural crest. HFSCs and MeSCs are normally quiescent except during early anagen, when they are activated concurrently to regenerate a pigmented hair[7,8]. Activation of HFSCs produces a new hair follicle. Activation of MeSCs generates differentiated melanocytes that migrate downwards, whereas MeSCs remain close to the bulge. At the hair bulb, differentiated melanocytes synthesize melanin to colour the newly regenerated hair from the root. At catagen, mature melanocytes are destroyed, leaving only the MeSCs that will initiate new rounds of melanogenesis in future cycles[9,10] (Extended Data Fig. 1a). The predictable behaviour of MeSCs and melanocytes, and the visible nature of hair colour, makes the melanocyte lineage an accessible model to investigate how stress influences tissue regeneration.

Diverse stressors induce hair greying

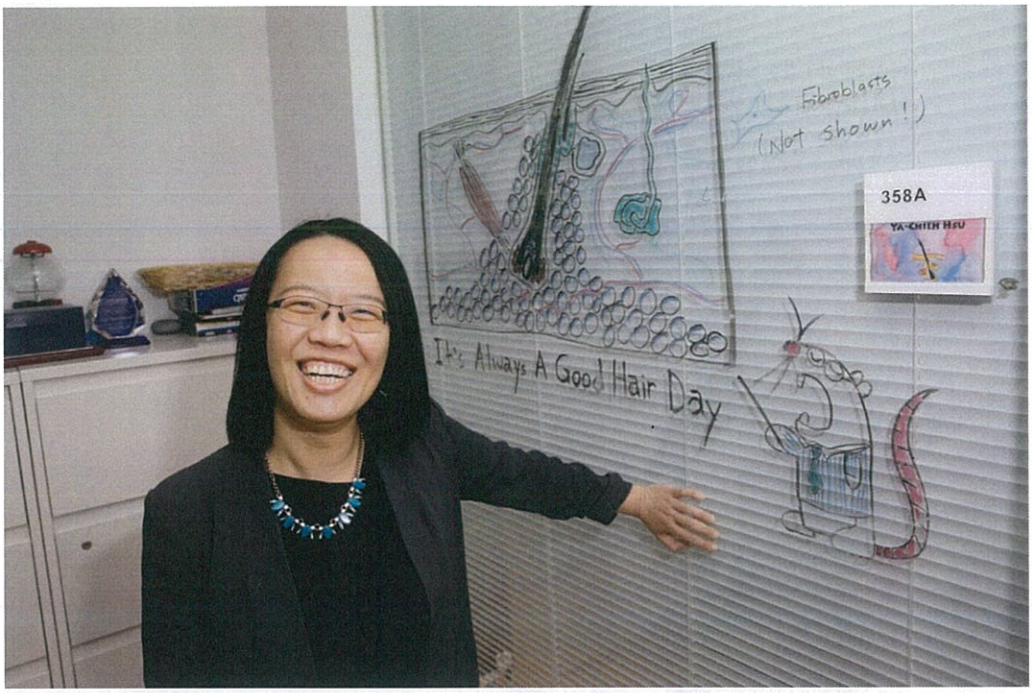
To examine whether psychological or physical stressors promote hair greying, we used three approaches to model stress in C57BL/6J mice with black coat colour: restraint stress[11,12], chronic unpredictable stress[13,14] and nociception-induced stress (which was achieved through an injection of resiniferatoxin (RTX), an analogue of capsaicin[15,16]). All three procedures led to increased numbers of unpigmented white hairs over time. Restraint stress and chronic unpredictable stress led to noticeable hair greying after three to five rounds of hair cycles. Nociception-induced stress produced the most pronounced and rapid effect—many new hairs that formed in the next hair cycle after RTX injection became unpigmented (Fig. 1a, b, Extended Data Fig. 1b, c).

Psychological or physical stressors trigger the adrenal glands to release stress hormones and catecholamines into the bloodstream[17]. In accordance with this, we detected an increase in both corticosterone (the primary glucocorticoid stress hormone in rodents that is equivalent to cortisol in humans) and noradrenaline (a catecholamine) in the blood of mice that were subjected to different stressors (Fig. 1c, Extended Data Fig. 1d), suggesting that our approaches induced classic stress responses.

[1]Department of Stem Cell and Regenerative Biology, Harvard University and Harvard Stem Cell Institute, Cambridge, MA, USA. [2]Klarman Cell Observatory, Broad Institute of MIT and Harvard, Cambridge, MA, USA. [3]Department of Biology and Koch Institute, Massachusetts Institute of Technology, Cambridge, MA, USA. [4]Cutaneous Biology Research Center, Department of Dermatology, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA, USA. [5]Department of Molecular and Cellular Biology, Harvard University, Cambridge, MA, USA. [6]Department of Immunology, Harvard Medical School, Boston, MA, USA. [7]Institute of Biological Science, Federal University of Minas Gerais, Belo Horizonte, Brazil. [8]Stem Cell Program and Division of Hematology/Oncology, Boston Children's Hospital and Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA. [9]Howard Hughes Medical Institute, Chevy Chase, MD, USA. [10]Center for Research in Inflammatory Diseases (CRID), Department of Pharmacology, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil. *e-mail: yachieh_hsu@harvard.edu



Credit: The Harvard Gazette



論文通訊作者**許雅捷**係本系 02 級系友，目前是美國哈佛醫學院幹細胞及再生生物學系 Alvin and Esta Star 講座副教授（Credit: Jon Chase/Harvard Staff Photographer）

專有名詞中文對照：

Stem Cell：幹細胞	Cortisol：皮質醇
Hair follicle：毛囊	Melanocyte：黑色素細胞
Sympathetic nervous system：交感神經系統	Pigment：色素
Analogue：類似物	Inhibitor：抑制劑
Capsaicin：辣椒素	Inflammation：發炎反應
Immune cells：免疫細胞	Arteries：動脈
Noradrenaline：正腎上腺素	Tissue：組織
Adrenal glands：腎上腺	Cholesterol：膽固醇

6. 在這篇報導中，缺失免疫細胞的老鼠在壓力情境下仍會產生毛色灰化的狀況，依文章中提供的資訊，請問最可能的解釋是？（單選）
   a. 缺失免疫細胞的老鼠因為感染而壓力更大
   b. 免疫細胞可能不會攻擊黑色素幹細胞
   c. 免疫細胞可能不會分化成黑色素細胞
   d. 免疫細胞可能不會造成毛囊的發炎反應
   e. 以上皆是
   f. 以上皆非

7. 在這篇報導中，移除腎上腺的老鼠在壓力情境下仍會產生毛色灰化的狀況，依文章中提供的資訊，請問最可能的解釋是？（單選）
   a. 腎上腺分泌的皮質醇是黑色素的前驅物
   b. 腎上腺分泌的皮質醇對老鼠並不會造成壓力反應
   c. 腎上腺分泌的皮質醇是黑色的
   d. 腎上腺分泌的皮質醇促進了黑色素的合成
   e. 腎上腺分泌的正腎上腺素干擾了黑色素幹細胞的分化
   f. 以上皆是
   g. 以上皆非

8. 在這個研究中，科學家發現交感神經造成毛色灰化的最可能解釋是？（單選）
   a. 交感神經讓黑色素幹細胞進行細胞自戕，導致黑色素幹細胞大量死亡
   b. 交感神經使幹細胞分化變快，導致黑色素幹細胞來不及在毛囊內補充
   c. 交感神經分泌神經傳導物質抑制了黑色素在角質細胞內的合成
   d. 交感神經促進了黑色素幹細胞的遷徙，讓黑色素幹細胞都集中到毛囊深處
   e. 以上皆是
   f. 以上皆非

9. 在這篇報導中，依文章中提供的資訊，科學家認為 CDK 抑制劑能夠改善毛色灰化，主要的理由是？（單選）
   a. CDK 抑制劑可能可以抑制幹細胞的分化
   b. CDK 抑制劑可能可以抑制皮質醇的分泌
   c. CDK 抑制劑可能可以讓老鼠不再感受到壓力
   d. CDK 抑制劑可能可以促進幹細胞的製造
   e. CDK 抑制劑可能可以抑制副交感神經分泌正腎上腺素
   f. 以上皆是
   g. 以上皆非

10. 在這篇報導中，科學家使用辣椒素的類似物來刺激老鼠，以你對生命科學實驗的瞭解，以下哪些實驗設計是不恰當的：（單選）
   a. 科學家必須使用施加安慰劑的控制組
   b. 在可能的情況下，科學家應該進行雙盲測試
   c. 科學家必須使用和實驗組有相同遺傳背景的老鼠作為控制組
   d. 科學家必須移除與預期結果不相符的樣本
   e. 以上皆是
   f. 以上皆非