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A new way to go gray

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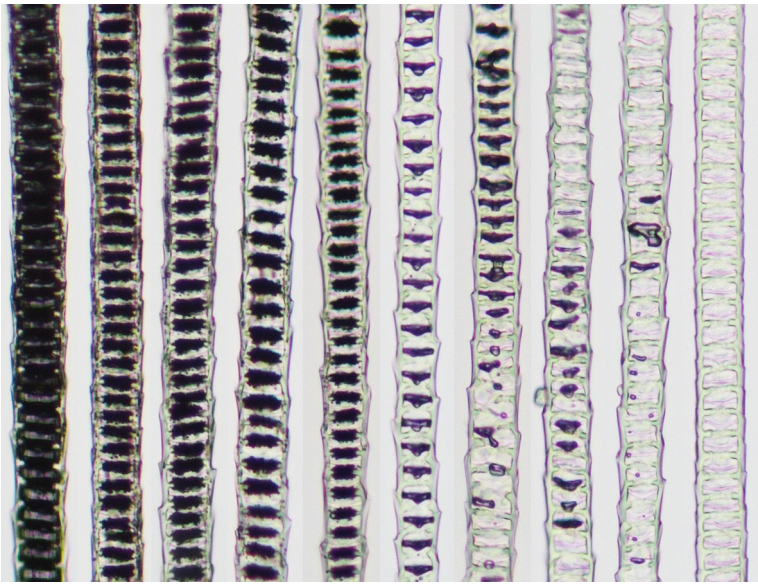
Anecdotally, there are lots of ways to go gray, but one that's really true has to do with how pigment cells in the hair deal with viral infection. In response to a virus, some of us may be better than others at keeping our colorful locks.



Progressive graying seen in hair shafts. Photo credit, Melissa Harris

Although gray hair is often seen as just another sign of getting older, for us at the Harris Lab it's a window into the mysterious world of stem cells and their role in aging and tissue regeneration. Hair color depends on a specialized set of cells called melanocytes that produce and deposit pigment into the hair shaft as it grows. Melanocytes derive from stem cells—melanocyte stem cells (McSCs), to be exact—that divide to produce new melanocytes each time an old hair falls out and is replaced by a new hair. Sadly, as we age, the McSC supply can be exhausted, which means no new melanocytes and thus no pigment in your hair. The final outcome is relatable to many of us past the fifth decade of life and is commonly referred to as "gray" or "white" hair.

As biologists, we're interested in the genes that control when, why and how much we gray as we get older. Genes can lead to the creation of proteins in varying amounts through a process called gene expression, and gene expression can have dizzyingly complex consequences in the cell. For melanocytes and their precursors, one particularly important gene is called MITF. Alterations in this gene and its protein in mice can have drastic effects on the function of melanocytes and McSCs, and therefore hair color. For example, we previously showed that taking mice that are slightly more genetically susceptible to getting gray hair (we'll call these "salt-and-pepper" mice) and engineering them to express only half the normal level of MITF (a trick we'll refer

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to as “half-MITF”) resulted in mice that became extremely gray, extremely early in life due to premature loss of their McSCs.

Curious about why the reduction in MITF expression is so detrimental to McSCs, we—in conjunction with researchers at NIH—examined data from typical McSCs and McSCs isolated from half-MITF mice. Surprisingly, the results showed a curious uptick in gene expression related to type I innate immune responses in the half-MITF mice. In a cell infected by a virus or pathogen, the type I innate immune pathway protects against further infection by releasing proteins called interferons. Akin to a cellular community watch program, the presence of interferons warns neighboring cells that a threat is present and prepares cells to defend themselves. This suggested that MITF is important in reducing the expression of certain immune genes. And it naturally led to the next question: what role did the immune response play in those previous research results involving the salt-and-pepper mice that were engineered to be half-MITF?

A compound called a viral mimic provided a straightforward way to study these questions. As the name suggests, administration of the mimic simulates a viral infection, triggering the type I innate immune response in mice. After plucking hairs from both salt-and-pepper mice and genetically ordinary mice to initiate new hair growth, the viral mimic was administered to the mice three days in a row. The mice were then visually inspected to compare hair color, and sections of their skin were analyzed by a combination of microscopy and cellular labeling. In the end, administering the viral mimic was not sufficient to cause hair graying in the genetically ordinary mice, but the salt-and-pepper mice showed a striking increase in the number of gray hairs in the area that was plucked. Moreover, the microscopy and cellular labeling revealed that this hair graying was the result of McSC and melanocyte depletion. Thus, the intriguing takeaway was that mice predisposed to early hair graying got much grayer when their type I innate immune response was increased—whether by a genetic alteration (half-MITF) or by exposure to a pathogen (viral mimic).

Although having gray hair doesn’t mean that you’re sick, the results of this study suggest that getting a virus could contribute to age-related hair graying, which raises interesting questions. Why were the salt-and-pepper mice affected differently? Are there hair graying susceptibility genes that function similarly in humans? Implicating the innate immune system in hair graying is also intriguing because studies have connected the autoimmune, pigmentation disease vitiligo to the innate immune response. As always, more questions than answers remain, but this study suggests a direct link between the innate immune system and hair graying.