

## **A new way to go gray.**

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Gray hair is generally bemoaned as just an inevitable sign of aging, but for the Harris Lab it's a window into the still mysterious life of stem cells and their role in aging and tissue regeneration. For people without gray hair, you can thank two specialized types of cells, the melanocytes and melanocyte stem cells (McSCs), for ensuring that your locks retain their characteristic hue. Melanocytes are spindly, colorful cells that reside within the base of each hair follicle and extend dendrites (which are akin to long arms) to deposit pigment into the hair shaft as it grows. Every time a hair falls out, the melanocytes go with it, and new melanocytes are generated by the McSCs that are associated with each hair follicle. You can imagine then that if your supply of McSCs gets depleted, it means no new melanocytes for your hair and thus gray (unpigmented) hair for you. Although the thought of more gray hair might make you feel sick, in the Harris Lab the study of gray-haired mice has led to new insights into the role of the immune system in hair graying and the link between the two rests more on a common protein than on your mental state (Harris et al., 2018).

This protein is called MITF. MITF stands for microphthalmia-associated transcription factor, a name which implies its function. A transcription factor is a type of protein that can bind to DNA and essentially turn a gene “on” or “off” in a process known as gene expression. MITF is best known for its ability to turn on the genes that are essential for the development of melanocytes. However, when our lab—in conjunction with researchers at NIH— analyzed a mouse that expressed half the normal amount of MITF (a state called “haploinsufficiency”), we also found a curious uptick in the expression of genes important in type I innate immune responses. In a cell infected by a virus or pathogen, the type I innate immune pathway protects against further infection by releasing 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 to us that MITF, beyond its known roles in pigmentation, may also play a role in reducing the expression of certain immune genes.

So, how does all of this relate to gray hair? We commonly use a type of genetically-altered mice that are susceptible to premature hair graying, called Tg(Dct-Sox10) mice, to help us identify genetic changes or treatments that have the power to prevent this process. Previously, we had unexpectedly found that the combination of Tg(Dct-Sox10) and haploinsufficiency for MITF greatly exacerbated the production of gray hair (Harris et al., 2013). Based on the observation from our current study that MITF represses innate immune gene expression, we wondered whether an elevated immune response in these mice is actually bad for their melanocytes and McSCs. As a way to confirm the role of innate immune activation in hair graying we took the same Tg(Dct-Sox10) mice and treated them with a compound called poly(I:C), which mimics viral infection. These mice showed comparatively worse graying than those that did not receive poly(I:C). By zooming in on the skin using microscopy and cellular

labeling, we found that graying in poly(I:C)-treated, Tg(DctSox10) mice is caused by a reduction in melanocytes and McSCs, a phenomenon that is not observed in non-susceptible mice treated with poly(I:C). In short, this suggests that messing with innate immune signaling, either via a genetic mechanism (like haploinsufficiency for MITF) or viral infection, can worsen gray hair in animals that are already predisposed for this condition. Why this is so—and the mechanism behind it—we cannot wait to figure out!

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, a conclusion that raises interesting questions. Why were the Tg(Dct-Sox10) mice affected differently from the non-susceptible mice, and are there hair graying susceptibility genes that function similarly in humans? Implicating the innate immune system in hair graying is also particularly intriguing in light of different studies that have connected the pigmentation disease vitiligo to the innate immune response and others that have observed a differential interferon-related gene expression in animals lacking a key receptor closely tied to MITF. As always, more questions than answers remain, but this study suggests a direct link between the innate immune system and hair graying.

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