RESEARCH ARTICLE SUMMARY

STEM CELLS

Hair follicle aging is driven by transepidermal elimination of stem cells via COL17A1 proteolysis

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INTRODUCTION: During aging, most organs in mammals become smaller (miniaturize) or thinner, and their functions and regenerative capability also decline. Histologically, tissue atrophy and fibrosis are observed in many aged organs. Yet the exact mechanisms for the architectural and functional decline are unknown. Indeed, areas that are as yet underexplored include the dynamics of the constituent cells and their cellular fate, as well as determination of whether aged or damaged cells accumulate or are eliminated in tissues and organs during the aging process. Organismal aging has been explained by various theories—such as reactive oxygen species, cellular senescence, telomere erosion, and altered metabolism—but not from the viewpoint of cellular and tissue dynamics. Stem cell systems sustain cellular and tissue turnover in most mammalian organs, but it has been difficult to experimentally test the precise fate of somatic stem cells, the cellular pool for tissues and organs. This has limited our understanding of the mechanisms of aging of tissues and organs and the existence of an aging program in mammalian organs. The hair follicle (HF) is an epithelial mini-organ of the skin that sustains cyclic hair regrowth over repeated hair cycles. Hair thinning (senescent baldness) is one of the most typical signs of aging in many long-lived mammals and is often prematurely induced by genomic instability, as in progeroid syndromes. We studied the mechanism for aging of the epithelial mini-organ.

RATIONALE: Miniaturization of HFs has long been believed to be a specific key phenomenon for male-pattern baldness (androgenic alopecia) but not for HF aging. Our study revealed that mammalian HFs do miniaturize and often disappear from the skin during aging both in mice and humans, regardless of sex. We employed in vivo stem cell fate tracing in mice during physiological aging and searched for possible links between the cell fate of aged HF stem cells (HFSCs) and the stepwise miniaturization and loss of HFs. Combining gene expression profiling of young versus aged HFSCs and conditional knockout or maintenance of gene expression in HFSCs in mice, we defined the early events and molecules that connect HF cycling, HFSC aging, and the dynamic HF aging processes, which are characterized by the stepwise miniaturization of HFs.

RESULT: The fate analysis of HFSCs during aging revealed that organ aging is primed by the sustained DNA damage response against DNA damage that accumulates in renewing stem cells during aging. This now tightly links intrinsic genomic instability in stem cells to epithelial organ aging. Further, we found that stem cell aging results from proteolysis of type XVII Collagen (COL17A1/BP180) by neutrophil elastase in response to DNA damage in HFSCs and the commitment of stem cells to epidermal differentiation. Terminal differentiation of HFSCs into epidermal keratinocytes drives HF miniaturization and enables the elimination of damaged stem cells as shed corneocytes from the skin surface. The fate of aged HFSCs abrogate their commitment to follicular differentiation to grow hair. Finally, HF aging can be recapitulated by *Col17a1* deficiency and can be prevented by the forced maintenance of COL17A1 in HFSCs. This demonstrates that COL17A1 in HFSCs orchestrates the stem cell–centric aging program of the epithelial mini-organ.

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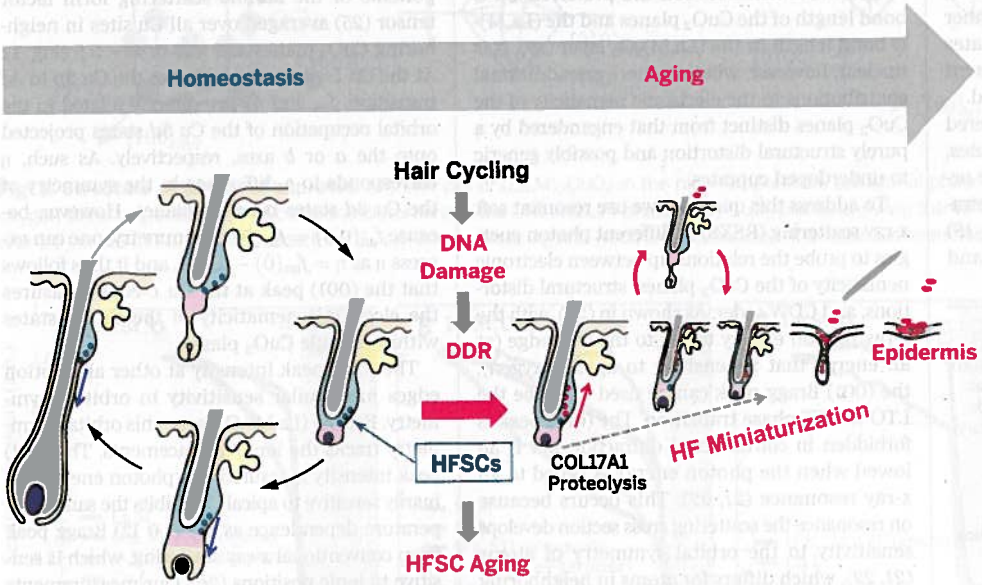
CONCLUSION: In vivo stem cell fate tracing of HFSCs revealed the critical role of HFSCs in the induction of aging-associated hair thinning. We identified a distinct organ aging program that is driven by transepidermal elimination of aged HFSCs through their depletion of COL17A1 via DNA damage–induced protease expression and terminal epidermal differentiation. The dynamic HF aging program is a good model of organ and tissue shrinkage and functional decline commonly seen in many different organs during aging. This paradigm could potentially open new avenues for the development of anti-aging strategies to prevent and treat aging-associated diseases. ■



The mechanism of HF aging and associated hair loss. HFs sustain their cyclic regeneration through the intensive self-renewal of activated HFSCs (blue dots). The aging of HFSCs is triggered by DNA damage-induced COL17A1 proteolysis. Once aged HFSCs (red dots) are activated during the hair cycle, they leave the niche and terminally differentiate into epidermal keratinocytes and are then eliminated from the skin surface.

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