

Center for Stem Cell Biology and Regenerative Medicine

Division of Stem Cell Aging Medicine

幹細胞加齢医学分野

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Stem cell systems play fundamental roles in sustaining tissue turnover and homeostasis. Our goal is to understand the mechanisms of tissue homeostasis in mammals and to apply that knowledge to better understand the mechanisms underlying tissue/organ aging, cancer development and other relevant diseases associated with aging. We further aim to apply this knowledge to drug discovery, regenerative medicine and the prevention and treatment of age-associated diseases.

1. Antagonistic stem cell fates under stress govern decisions between hair greying and melanoma.

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The accumulation of an individual's lifelong environmental exposure, known as the "exposome," significantly impacts tissue health, leading to divergent outcomes such as degenerative aging or cancer. Based on our previous finding that genotoxic stresses drive hair graying, our recent study published in *Nature Cell Biology* (2025) identified critical fate determinations in melanocyte stem cells (McSCs) under genotoxic stresses. Using in vivo lineage tracing and gene expression profiling of McSCs, we demonstrated that double-strand breaks (DSBs) typically trigger a process termed "seno-differentiation" (senescence-coupled differentiation) via the p53-p21 pathway. This mechanism induces damaged McSCs to differentiate with stable cell cycle arrest and exit the niche, resulting in the exhaustion of the stem cell pool and subsequent hair graying. This process acts as a natural senolysis, eliminating potential cancer founder clones from the tissue as a protective mechanism. Converse-

ly, we found that this protective program can be bypassed when McSCs are exposed to carcinogens, such as UVB or DMBA, which stimulate the expression of the niche-derived KIT ligand (KITL). The signal suppresses senescence even in cells harboring DSBs, promoting their survival, which ultimately increases the susceptibility of the tissue to melanomagenesis. Collectively, our findings reveal that the stem cell niche acts as a master regulator that determines the fate of individual McSCs. This antagonistic bifurcation between exhaustion vs. expansion cumulatively determines the fate of the tissue, manifesting phenotypically as hair graying or melanoma, depending on the nature of the exposome. We are now expanding this conceptual framework to investigate whether similar molecular systems govern the fate of other somatic stem cell populations. Our goal is to further bridge the gap of our understandings between tissue aging and cancer development.

2. TLR7 responses to nucleosides drive sialadenitis in *Slc29a3*-deficient mice

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Autoimmune sialadenitis is a hallmark of IgG4-related disease (IgG4-RD) and Sjögren syndrome (SS). The single-stranded RNA sensor TLR7 has been shown as a driver of sialadenitis. Although TLR7 is activated by ssRNA degradation products such as nucleosides and oligoribonucleotides, the role of these ligands in sialadenitis development remains unclear. Here, we demonstrate that lysosomal accumulation of endogenous nucleosides is sufficient to drive autoimmune sialadenitis. Loss-of-function genetic variations in the nucleoside transporter *SLC29A3* cause lysosomal nucleoside accumulation, leading to constitutive activation of TLR7 and TLR8 in monocytes and macrophages. Consequently, macrophages infiltrate multiple organs in mice and humans. In *Slc29a3*^{-/-} mice, submandibular glands (SMGs) were impaired in saliva production. *SLC29A3*-deficiency specifically damaged Aqp5⁺ acinar and intercalated duct cells in SMGs, while sparing neighboring cells such as ductal and myoepithelial cells. Although macrophages accumulated in both the spleen and SMGs, lymphocyte infiltration and production of chemokines including CXCL9, CXCL13, and CCL5 occurred selectively in SMGs. In IgG4-RD patients, these chemokines were also produced in SMGs, highlighting parallels between sialadenitis in *Slc29a3*^{-/-} mice and IgG4-RD. These findings indicate that constitutive TLR7 activation by nucleosides is a key mechanism driving autoimmune sialadenitis.

Publication

1. Mohri Y, Nie J, Morinaga H, Kato T, Aoto T, Yamanashi T, Nanba D, Matsumura H, Kirino S, Kobiyama K, Ishii KJ, Hayashi M, Suzuki T, Nami-ki T, Seita J and Nishimura, EK. Antagonistic stem cell fates under stress govern decisions between hair greying and melanoma. *Nat Cell Biol.* 10:1647-1659, 2025.
2. Shibata T, Okabe-Kibe K, Chen H, Yamaguchi K, Koga D, Taoka M, Motoi Y, Sato R, Hsiao HW, Fukui R, Kaneko N, Wang Z, Li Y, Wei W, Cai Z, Furukawa Y, Nishimura E, Kawano S, Moriyama M, Nakamura S, Miyake K. TLR7 responses to nucleosides drive sialadenitis in *Slc29a3*-deficient mice. *Int Immunol.* in press. doi: 10.1093/intimm/dxaf073.
3. Mohri Y and Nishimura EK. Senescence-coupled differentiation selectively eliminates cancer-prone stem cells. *Nature Cell Biology, Research Briefing*, 27: 1605–1606 (2025)