Department of Cancer Biology

Division of Aging and Regeneration
老化再生生物学分野

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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. Stem cell fate governs hair graying and melanoma development

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The accumulation of an individual's lifelong environmental exposure, known as the "exposome", has a significant impact on health. Somatic tissues undergo functional decline with age, exhibiting characteristic ageing phenotypes such as hair graying and cancer. However, specific genotoxins and signals driving each phenotype and their underlying cellular mechanisms remain largely unknown. Importantly, DNA damage foci are relatively frequently found in somatic stem cells in the skin during physiological aging. Using a DNA damage inducing model, we previously found that the induction of DNA double strand breaks (DSBs) advances the expression of aging phenotypes including hair graying. To study the fate and dynamics of DNA-damaged stem cells in tissues and the resultant impact in the expression of aging phenotypes, we first focused on the melanocyte lineage and traced the fate of melanocyte stem cells (McSCs) which acquired DNA DSBs and demonstrated that

those cells disappear from the niche, causing the loss of mature melanocytes for hair pigmentation.

We studied the impact of DSBs in McSCs and found that McSCs and their niche coordinately determine individual stem cell fate through antagonistic, stress-responsive pathways, depending on the type of genotoxic damage incurred. Chronological stem cell fate-tracking in mice revealed that McSCs undergo cellular senescence-associated differentiation (seno-differentiation) in response to DSBs and downstream signaling, resulting in their selective depletion and hair graying, effectively acting as a protective mechanism against melanoma development. Conversely, carcinogens can suppress McSC seno-differentiation, even in DSB-harboring cells, by activating KITL (KIT ligand), a master niche factor for McSC self-renewal. Collectively, our data demonstrate that the fate of individual stem cell clones - expansion versus exhaustion - cumulatively and antagonistically governs a degenerative ageing phenotype and/or cancer development through the stem cell niche, depending on the exposome. We are currently testing whether DNA DSBs in other stem cells similarly promotes degenerative tissue aging.

2. Elucidating the molecular mechanisms underlying Sialadenitis

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We humans are continuously exposed to diverse stressors such as radiation, ultraviolet light, and infections, and homeostasis is maintained by stress responses triggered by cells detecting these challenges. However, dysregulated or excessive stress responses can lead to various diseases and accelerate aging. Under stress conditions, characteristic molecular patterns that are normally absent in the body emerge. Pathogen-derived molecules are termed PAMPs (Pathogen-Associated Molecular Patterns), whereas self-derived molecules released during cell death are known as DAMPs (Damage-Associated Molecular Patterns). Nucleic acids and their metabolites also function as PAMPs or DAMPs, and their accumulation under such conditions gives rise to "nucleic acid stress." Our research has focused on nucleic acid sensors that detect this stress, and we have demonstrated that excessive activation of these sensors can lead to autoimmune diseases and histiocytosis. In contrast, the role of nucleic acid sensors in the aging process remains largely unknown. Recently, the lead author found that genetically engineered mice with hyperactivation of the single-stranded RNA sensor TLR7 readily develop sialadenitis. The reduction in saliva production directly leads to xerostomia (dry mouth), a hallmark of aging that contributes to dental caries, periodontal disease, and taste disorders, ultimately resulting in a significant long-term decline in quality of life (QOL). However, due to the unclear molecular mechanisms underlying xerostomia, current treatments for sialadenitis are limited to symptomatic management. Based on insights gained from these sialadenitis model mice, we aim to develop a comprehensive understanding of xerostomia and ultimately elucidate the molecular mechanisms underlying salivary gland aging.

Publications

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