

論文概要

○ 論文題目

Wild-type and SAMP1/8 mice show age dependent changes in distinct stem cell compartments of the interfollicular epidermis
(野生型老齡マウスと老化促進マウス (SAMP1/8) を用いた表皮幹細胞の老化表現型の解析)

○ 指導教員

人間総合科学研究科 Biomedical Sciences 専攻 Dr. Hiromi Yanagisawa 教授

所属：

Graduate School of Comprehensive Human Sciences in University of Tsukuba
Doctoral Program in Biomedical Sciences

氏名： CHANGARATHIL GOPAKUMAR

Abstract

Purpose: Delayed wound healing and reduced barrier function with an increased risk of cancer are characteristics of aged skin and one possible mechanism is misregulation or dysfunction of epidermal stem cells during aging. Recent studies have identified heterogeneous stem cell populations in the mouse interfollicular epidermis that are defined by territorial distribution and cell division frequency; however, it is largely unknown whether individual stem cell populations undergo distinct aging processes. My research aims to understand the cellular and molecular basis of stem cell aging in the mouse epidermis with a special focus on two populations of stem cells that divide at different rates.

Materials and methods: The tail epidermis was chosen as a model to study the stem cell aging, because of the presence of regionally-defined scale and interscale structures, corresponding to the localization of slow-cycling and fast-dividing stem cells, respectively. C56BL6/J wild-type mice at ages of 2 months (young) and 2 years (old), as well as SAMR, SAMP1 and SAMP8 mice at 6 months and 1 year of age were used for the aging phenotype characterization. Young and old H2B-GFP tet-off mice were used to study the proliferation history, cell isolation and the transcriptome analysis of slow-cycling and fast-dividing stem cells in the interfollicular epidermis.

Results: The epidermis exhibits structural changes such as irregular undulations and overall thinning of the tissue in old wild-type mice. In the old epidermis, proliferation is preferentially decreased in the region where fast-dividing stem cells reside whereas the lineage differentiation marker appears to be more affected in the slow-cycling stem cell region. The quantitative analysis of proliferation history by using H2B-GFP tet-off system further supports that in the

old epidermis, all the basal cells are slower-cycling compared to the ones in the young epidermis. Furthermore, SAMP8, but not SAMP1, exhibits precocious aging similar to that of aged wild-type mice at 1 year of age, suggesting a potential use of this model for aging study of the epidermis and its stem cells. Finally, RNA sequencing of slow-cycling and fast-dividing stem cells reveals that genes related to extracellular matrix and cellular metabolism are over represented in the aged stem cells.

Discussion: Previous studies point out that young and old epidermis are transcriptionally and architecturally similar. My study here provides evidence regarding the age-dependent changes in the murine epidermis. I showed that slow-cycling and fast-dividing stem cells of the epidermis seem to be affected in different aspects of tissue maintenance: differentiation process appears to be affected in the slow-cycling stem cell lineage, whereas proliferation is affected in fast-dividing stem cells. Moreover, gene expression profiling between young and old epidermal stem cells reveals specific gene sets which are up- or down-regulated during aging, pointing out that the aged epidermis exhibits transcriptional changes at the stem cell level.

Conclusion: Taken together, my study reveals distinct aging processes governing the two epidermal stem cell populations and suggests a potential mechanism in differential responses of compartmentalized stem cells and their niche to aging.