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学位の種類	博士（医学）
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審査研究科	人間総合科学研究科
学位論文題目	Wild-type and SAMP1/8 mice show age dependent changes in distinct stem cell compartments of the interfollicular epidermis （野生型老齢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）

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論文の内容の要旨
Abstract of thesis

In this doctoral dissertation, CHANGARATHIL GOPAKUMAR describes the aging of the heterogeneous stem cell populations in the mouse interfollicular epidermis. The summary is as follows:

（目的　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 heterogenous 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 process. In this research, the author 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.

（対象と方法　Materials and Methods）

The author chose the tail epidermis 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. C57BL6/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.

（結果　Results）

The epidermis exhibited structural changes such as irregular undulations and overall thinning of the tissue in old wild-type mice. In the old epidermis, proliferation was preferentially decreased in the region where fast-dividing stem cells reside whereas the lineage differentiation marker appeared 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 supported that in the old epidermis, all the basal cells were slower-cycling compared to the ones in the young epidermis. Furthermore, the author noted that SAMP8, but not SAMP1, exhibited precocious aging similar to that of aged wild-type mice at one year of age, suggesting a potential use of this model for aging study of the epidermis and its stem cells. Finally, by means of RNA sequencing of slow-cycling and fast-dividing stem cells, the author demonstrated that genes related to extracellular matrix and cellular metabolism were overrepresented in the aged stem cells.

（考察　Discussion）

The author discusses that while previous studies pointed out that young and old epidermis are transcriptionally and architecturally similar, this study here provides evidences regarding the age-dependent changes in the murine epidermis. 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, the author emphasizes that gene expression profiling between young and old epidermal stem cells revealed 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.

Taken together, the author considers that this study revealed distinct aging processes governing the two epidermal stem cell populations, and suggested a potential mechanism in differential responses of compartmentalized stem cells and their niche to aging.

審査の結果の要旨
Abstract of assessment result

（批評　General Comments）

Changarathil Gopakumar examined the differences in proliferative potencies and gene expression profiles of two distinct interfollicular stem cells in young and old mice epidermis. He found the differences of aged phenotypes between two stem cell populations: *i.e.*, changes in the differentiation process of the slow-cycling stem cell lineage and in the proliferation of fast-dividing stem cells. He further found that SAMP8 but not SAMP1 mice exhibit precocious aging similar to that of aged wild-type mice. The research is original and appropriately designed. Data are clear and convincing and the discussion is reasonable. The thesis paper is carefully written with a suitable style.

（最終試験の結果　Assessment）

The final examination committee conducted a meeting as a final examination on June 17, 2019. The applicant provided an overview of dissertation, addressed questions and comments raised during Q&A session. All of the committee members reached a final decision that the applicant has passed the final examination.

（結論　Conclusion）

The final examination committee approved that the applicant is qualified to be awarded Doctor of Philosophy in Medical Sciences.