Physiological Genetics Laboratory
Chief Scientist: Sa Kan Yoo (M.D., Ph.D.)

(0) Research field

CPR Subcommittee**:** Biology

Keywords:

Tissue repair, cancer stress, tissue homeostasis, aging, nutrition

(1) Long-term goal of laboratory and research background

Living organisms can cope with disruption of homeostasis such as injury and disease to a certain degree. This results in restoration of steady state homeostasis, death of affected tissues or ultimate organismal death. The outcome depends on the type of insults, species of animals and maturation of tissues. While the process is well recognized, we still do not know the mechanisms defining responses to disruption of homeostasis in different organs and species. Our research focuses on three fundamental questions targeting major disruption of homeostasis in organisms: 1) How do animals repair tissues upon injury? 2) How does oncogenic stress by cancer affect animals? 3) What is the mechanism of aging? To do this, we utilize unrivaled genetics of the fruit fly, Drosophila melanogaster.

(2) Current research activities (FY2021) and plan (until Mar. 2025)

(1) How does oncogenic stress by cancer kill animals?

So much study has been done on cancer itself, such as how cancer occurs, grows and metastasizes. However, systemic effects of local cancer on the host remain undefined. We investigate how cancer affects and kills the host animals. Traditionally, infection, hemorrhage or organ failure has been used as explanation of cancer death, but in fact many patients can become weak without any of these. Clinically, some cytokines such as TNF are upregulated in cancer patients, but none of the inhibitors for these cytokines were effective to prevent the systemic effects of cancer. We are elucidating the mechanisms by which cancer affects the host animals using *Drosophila*. Since I started my lab in 2015, we already established various genetic systems in which we can induce cancer and make flies die. Using this system, we have been performing genetic screening using EMS mutagenesis and RNAis, RNAseq and metabolomics. We found several key genes and metabolites that are critical for systemic effects of cancer.

(2) How does aging affect physiology in animals?

We have been trying to elucidate the fundamental mechanism of aging using *Drosophila*. We are focusing on several phenotypes that occur during aging: 1) stem cell dysplasia in the gut, 2) wound healing defect in epithelia and muscles, 3) developmental origin of aging, 4) screening of super long-lived animals. Regarding stem cell dysplasia that occurs during aging, we identified an ABC transporter that is responsible for it and published the result (Sasaki et al. Nature Metabolism 2021). Regarding the wound healing defect, we published a key mechanism of wound healing previously (Yoo et al. Nature communications, 2016). Now we are investigating effects of aging on wound repair. On developmental origin of aging, we found that specific nutritional conditions during development have effects that only manifest during aging. Regarding the screening of super long-lived animals, we already identified mutants that live unusually long. We are in a process to identify responsible genes for their longevity by whole genome sequencing.

(3) Mechanisms of cell turnover and cell death in tissue homeostasis

Tissues have mechanisms to maintain their homeostasis under physiological conditions and emergent situations. Detailed mechanisms by which tissue homeostasis is accomplished in organs still remain elusive. For example, many tissues remain in a state of flux through life by combining apoptosis of differentiated cells and continuous proliferation of stem cells. But why differentiated cells die readily and stem cells are immortal remains unclear. We have been addressing the following questions: 1) why do epithelial cells of the gut die every 3-4 days?, 2) why are intestinal stem cells immortal?, 3) identification of new regulators of cell death. This year, we reported a novel cell death we named erebosis in Plos Biology (Ciesielski et al. 2022). We also discovered how oncogenes drive cell death and proliferation simultaneously (Nishida et al. eLife 2021). We are also performing an RNAi screening to identify factors that are responsible for enterocyte turnover in the gut. We identified a novel gene “sayonara” that regulates apoptosis. Intriguingly sayonara induces apoptosis in differentiated cells but proliferation in stem cells.

(3) Members as of March, 2021

福本	敬子	本務	アシスタント	常勤	Yoo 生理遺伝学研究室
高野	智美	兼務	特別技術員	非常勤	Yoo 生理遺伝学研究室
Yoo	Sa Kan	兼務	主任研究員	非常勤	Yoo 生理遺伝学研究室
岡田	守弘	兼務	研究員	非常勤	Yoo 生理遺伝学研究室

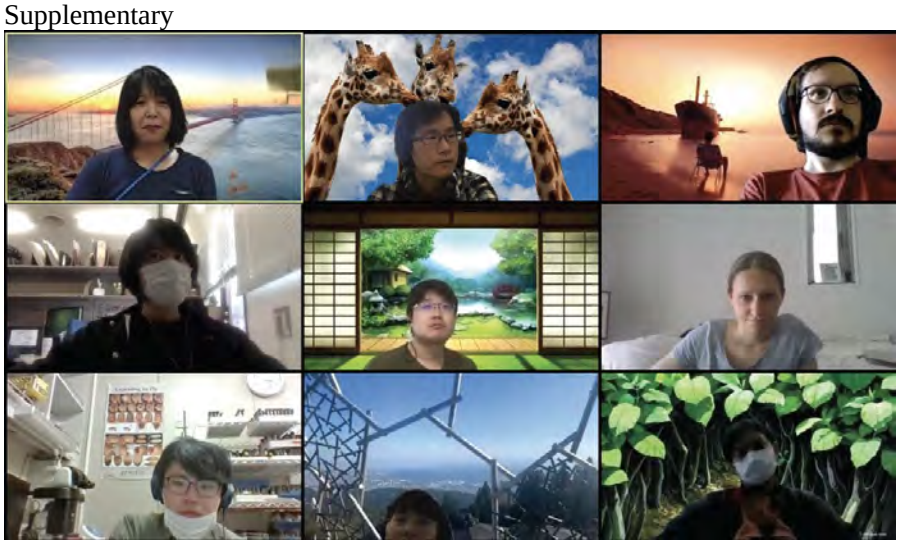
(4) Representative research achievements

Sasaki A, Nishimura T, Takano T, Naito S, **Yoo SK.** white regulats proliferative homeositasis of intestinal stem cells during ageing in Drosophila. ***Nature Metabolism*.** 2021 Apr 5 doi: 10.1038/s42255-021-00375-x.

Nishida H, Okada M, Yang L, Takano T, Tabata S, Soga T, Ho DM, Chung J, Minami Y, **Yoo SK.** Methionine restriction breaks obligatory coupling of cell proliferation and death by an oncogene Src in *Drosophila*. ***eLife*** 2021 Apr 27;10:e59809. doi: 10.7554/eLife.59809.

Ciesielski HM, Nishida H, Takano T, Fukuhara A, Otani T, Ikegawa Y, Okada M, Nishimura T, Furuse M, **Yoo SK**. Erebosis, a new cell death mechanism during homeostatic turnover of gut enterocytes. ***Plos Biology*** Apr 25;20(4):e3001586. doi: 10.1371/journal.pbio.3001586.

Supplementary



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