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 (FY2020) 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 we are currently preparing a paper for publication. 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. To address these questions, we are making a genetically encoded “timer” to label the age of cells. 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.

Future plans

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

Based on RNAseq, EMS mutagenesis, RNAi screening and metabolomics, we have already identified key genes

and metabolites that are involved in systemic responses to cancer. We also identified the fat body, which corresponds to the mammalian adipose and liver tissues, is a key organ that controls the systemic response to cancer. In the future, we will elucidate detailed mechanisms by which the identified key factors mediate the responses to cancer stress.

(2) How does aging affect physiology in animals?

We will address the mechanisms of the four aging processes described above. We will achieve a better understanding of both genetic and non-genetic mechanisms that regulate the aging process in whole animals.

1) Stem cell dysplasia in the gut

We already found that an ABC transporter is responsible for intestinal stem cell dysplasia that occurs during aging. We will identify metabolites that mediate the effect of the ABC transporter during aging.

2) Wound healing defect in epithelia and muscles

We found that JNK and Hippo signaling are involved in the wound healing defect during aging. We will identify upstream signaling of JNK and Hippo that is involved in the aging effect on wound repair.

3) Developmental origin of aging

We identified that developmental conditions mainly affect glycolysis in adult animals. We will further elucidate how developmental conditions leave a perdurant effect to glycolysis.

4) Screening of super long-lived animals.

We will identify genes that are responsible for long lifespan of long-lived flies.

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

1) Why do epithelial cells of the gut die every 3-4 days?

We will optimize our genetically encoded “timer” to label the age of cells. We will also complete the RNAi screening to identify factors that are responsible for enterocyte turnover in the gut.

2) Why are intestinal stem cells immortal?

We found that a gene rpr that inhibits DIAP is a key determinant that defines immortality of stem cells. We will identify why intestinal stem cells are very resistant to the apoptotic signal by rpr.

3) Identification of new regulators of cell death.

We identified a novel gene “sayonara” that regulates apoptosis. Intriguingly sayonara induces apoptosis in differentiated cells but proliferation in stem cells. We will further analyze how sayonara regulates cell death.

(3) Members as of March, 2021

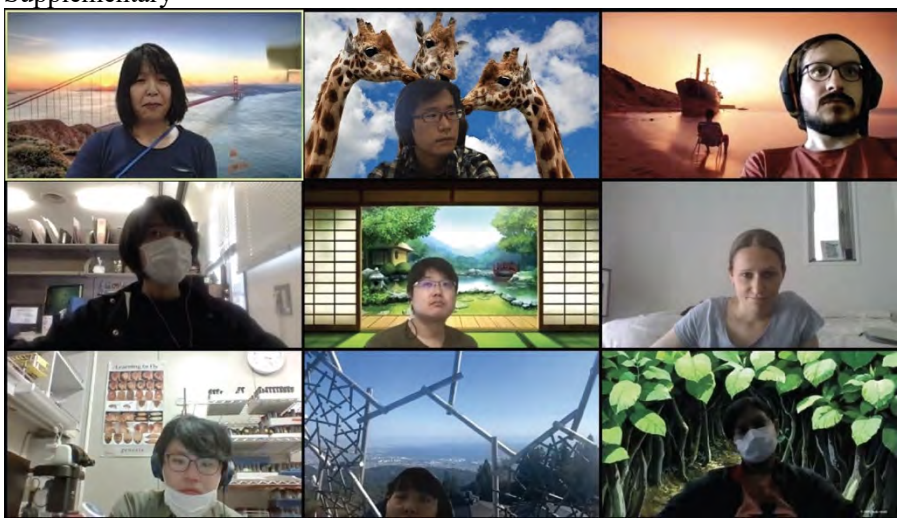
(Chief Scientist)
Sa Kan Yoo
(Research Scientist)
Morihiro Okada
(Special technical staff)
Tomomi Takano
(International Program Associate)
Hanna Ciesielski
(Junior Research Associate)
Hiroshi Nishida
(Assistant)
Keiko Fukumoto

(4) Representative research achievements

Ayaka Sasaki, Takashi Nishimura, Tomomi Takano, Saki Naito, Sa Kan Yoo.
white regulates proliferative homeostasis of intestinal stem cells during ageing in Drosophila
Nature metabolism. 2021 Apr 5. doi: 10.1038/s42255-021-00375-x

Hiroshi Nishida, Morihiro Okada, Lynna Yang, Tomomi Takano, Sho Tabata, Tomoyoshi Soga, Diana M Ho, Jongkyeong Chung, Yasuhiro Minami and Sa Kan Yoo
Methionine restriction breaks obligatory coupling of cell proliferation and death by an oncogene Src in Drosophila, eLife, in press

Supplementary



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