Science and Technology Group
Annual Report FY2025

Yohsuke Moriyama
Science and Technology Associate

Introduction

Cellular wounding and repair of local plasma membranes occurs constantly in our bodies. Plasma membrane damage (PMD) can be induced by various triggers ranging from physical disruption and pathogen invasion to physiological cellular activities, such as muscle contraction, cell division, and the secretion of vesicles. Accumulating evidence suggests the involvement of cellular wound healing in various diseases. However, the detailed physiological consequences of plasma membrane repair are poorly understood. We recently discovered that plasma membrane damage activates a cell cycle checkpoint in yeast, resulting in cell cycle arrest during plasma membrane repair (Kono et al., Proc. Natl. Acad. Sci. U. S. A., 2016).

Furthermore, we also found that the plasma membrane damage induces permanent cell cycle arrest and senescent phenotypes in the cultured mammalian cell. Permanent cell cycle arrest is characterized by its specific metabolic activity and dramatic changes in cell morphology.

Originally, it was proposed to be due to the shortening of telomeres after the repeated proliferation. Now that it is known that the cell cycle arrest is also induced by DNA damage response (DDR), oncogene expressions and several stresses. In addition to them, I and my collaborators have proven that the plasma membrane damage also triggers cellular senescence. (Suda*, Moriyama*, Nurhanani* et al., Nat aging, 2024 (*equal contribution))

Activities and Findings

Using budding yeast and normal human fibroblasts, we show that cellular senescence, irreversible cell cycle arrest contributing to organismal aging, is the long-term outcome of PMD. To identify the genes essential for PMD response, we developed a simple PMD-damaging assay using a detergent and performed a systematic yeast genome-wide screen. The top hits in the screen are the endosomal sorting complexes required for transport (ESCRT) genes, encoding the well-described plasma membrane repair proteins in eukaryotes. Unexpectedly, the replicative lifespan regulator genes are enriched in our 48 hits. This finding suggests a close genetic association between the PMD response and the replicative lifespan regulations. Indeed, we show that PMD limits the replicative lifespan in budding yeast; the ESCRT activator AAA-ATPase VPS4-overexpression extends it. These results suggest that PMD limits replicative lifespan in budding yeast. Moreover, in normal human fibroblasts, we find that PMD induces premature senescence via the Ca^{2+}-p53 axis but not the major senescence pathway, ATM/ATR pathway. Consistent with the results in yeast, transient overexpression of ESCRT-III, CHMP4B, suppressed the PMD-dependent senescence in normal human fibroblasts. Our study proposes that PMD limits cellular lifespan in two different eukaryotic cell types and highlights an underappreciated but ubiquitous senescent cell subtype, namely PMD-dependent senescent cells.

Senescent cells exhibit the senescence-associated secretory phenotype (SASP), a pathological feature that contributes to organismal aging. We previously showed that transient plasma membrane damage (PMD) induces a novel subtype of cellular senescence (PMDS) accompanied by SASP, but the overall expression profiles of SASP during PMDS induction was unknown. Using mRNA-seq, qPCR, and bioinformatics, we revealed the time-resolved SASP transcriptomic profile in PMDS in comparison with calcium influx-induced senescence, DNA damage response-induced senescence, and replicative senescence. SASP is diverse at early senescence and becomes relatively uniform at late senescence among the different senescence triggers. Diverse SASP may contribute to senescent cell subtype-specific paracrine/autocrine functions in vivo. These works were published in the Nature Aging.

Science and Technology Group
Annual Report FY2025

Yohsuke Moriyama
Science and Technology Associate

Collaborations

Prof. Keiko Kono (Kono Unit, OIST)
Dr. Nurhanani Razali, Dr. Kojiro Suda, Dr. Hunter Barbee, Yatzu Chiu (Kono Unit, OIST)
Prof. Hiroki Ishikawa, Masato Hirota (Ishikawa Unit, OIST)
Prof. Tadashi Yamamoto and Aisulu Maipas (Yamamoto Unit, OIST)
Tara Helmi Trukki (OIST)
SUNTORY Wellness, ltd

Publications and other output

Chiu Y, Ishida R, Moriyama Y, Grašič J, Kono K.
Time-resolved miRNA-mRNA integrated analysis reveals the miRNA-mRNA networks underlying plasma membrane damage-dependent senescence and DNA damage response-dependent senescence in WI-38 normal human fibroblasts.
RNA Biol. 2025 Dec;22(1):1-19.
doi: 10.1080/15476286.2025.2551299.

Fukasawa M, Hata T, Moriyama Y, Johkura K, Atsuzawa K, Higuchi S, Usuda N, Takahashi K and Nakai S
Activation of the reward system in the rat brain by moxibustion
In revision

Turkki T, Suda K, Moriyama Y, Chiu Y, Razali N, Kono K
A regulatory node in the transcriptional network underlying multiple senescence subtypes in WI-38 human fibroblasts
In revision

Suda K,Aoyama-Ishiwatari S, Nakamura K, Moriyama Y, Hirabayashi Y, Kono K
Ca2+ influx induces mitochondria-ER contact formation by MTCH1 to maintain Ca2+ homeostasis and cell viability
In revision

Lecture/Oral Presentation

Yohsuke Moriyama
The Mechanisms of Cellular Aging and the Potential of Functional Supplements, 9-Nov-2025
Japan Society of Nutrition and Food science, Kyusyu branch meeting 2025

Outreach activities

Yohsuke Moriyama	28-Apr-2025	Science lecture, Onna elementary school 5th graders
Yohsuke Moriyama	05-Aug-2025	OIST Children's School of Science, 3rd and 4th graders
Yohsuke Moriyama	23-Dec-2025	Science talk, Okinawa Nambu Shogyo high school