Science and Technology Group
Annual Report FY2023

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1 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))

2 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.

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3 Collaborations

Prof. Keiko Kono (Kono Unit, OIST)
Dr. Nurhanani Binti Razali, Dr. Kojiro Suda, Dr. Hunter Barbee, Yatzu Chiu (Kono Unit, OIST)
Dr. Arora Jigyasa (University of California, Berkeley)
Prof. Hiroki Ishikawa, Masato Hirota (Ishikawa Unit, OIST)
Prof. Tadashi Yamamoto and Aisulu Maipus (Yamamoto Unit, OIST)
Tara Helmi Trukki (OIST)
Prof. Junichi Ikenouchi, Dr. Atsushi Matsumoto (Kyushu University)
SUNTORY Wellness, ltd

4 Publications and other output

Suda K#, Moriyama Y#, Razali N#, Chiu Y, Masukagami Y, Nishimura K, Barbee H, Takase H, Sugiyama S, Yamazaki Y, Sato Y, Higashiyama T, Johmura Y, Nakanishi M, and Kono K*. Plasma membrane damage limits replicative lifespan in yeast and induces premature senescence in human fibroblasts. (2024) Nature Aging. (#: equal contribution)
DOI: https://doi.org/10.1038/s43587-024-00575-6
Featured on the cover. Introduced in News and Views and Spotlight.

Kono K and Moriyama Y
細胞膜損傷を起点とする新たな老化細胞サブタイプ (A novel senescent cell subtype triggered by plasma membrane damage) (2023) Igaku no Ayumi
DOI: https://doi.org/10.32118/ayu28705327

Oral and Poster Presentations

International

Chiu Y, Moriyama Y and Kono K."Time-resolved miRNA-mRNA Integrated Analysis Revealed the miRNA-mRNA Networks underlying the Cellular Senescence in Normal Human Fibroblasts" (2023 May), RNA2023, Singapore.

Grašič J, Suda K, Razali N, Taoufiq Z, Chiu Y, Moriyama Y, KonoK. "Time-resolved proteomic profiling of plasma membrane damage-dependent senescence reveals upregulation of wound healing response at the early stage of senescence" (2023 Oct), ICSA2023, Minnesota.

Razali N, Moriyama Y, Chiu Y, Suda K, and Kono K. "Time-resolved transcriptomic profiling of senescence-associated secretory phenotype (SASP) in multiple senescent cell subtypes" (2024 Jan) A3 Foresight program, Cellular Senescence: from Pathophysiology to Treatment. Osaka.

Grašič J, Suda K, Razali N, Taoufiq Z, Chiu Y, Moriyama Y, Kono K. "Time-resolved proteomic profiling of plasma membrane damage-dependent senescence reveals upregulation of wound healing response at the early stage of senescence (2024 Jan) A3 Foresight program, Cellular Senescence: from Pathophysiology to Treatment. Osaka.