Science and Technology Group
Annual Report FY2021

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1 Introduction

Cellular wounding and repair of local plasma membranes occurs constantly in our bodies. Plasma membrane damage 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, resulting in transient or permanent arrest of the cell cycle during plasma membrane repair (Kono et al., Proc. Natl. Acad. Sci. U. S. A., 2016). Furthermore, the damaged site memories the membrane damage as a small tubular bud on the outer surface of plasma membrane, and it affects transient or prominent cell cycle arrest depending on the plasma membrane damage quantities. 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.

2 Activities and Findings

I can't provide details here due to the pre-publication stage of the study, but I start with the examination of the importance of calcium for the membrane repair. By depleting or reducing the amount of extracellular calcium, human cell cells showed acute rupture after membrane damage introducing treatment (Fig.1).

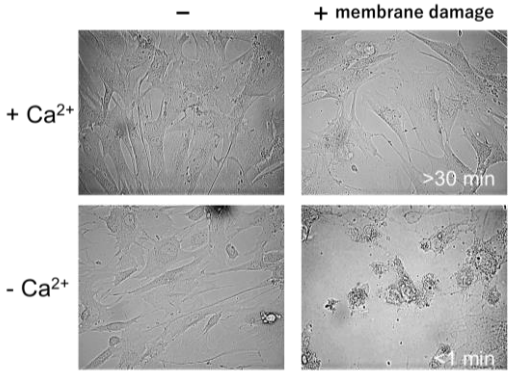

Figure1 Membrane repair ability is necessary for cell survival. When the culture condition lacks extracellular calcium, acute rupture of plasma membrane was observed.

Then, I have confirmed that transient plasma membrane damage treatment induced permanent cell cycle arrest in human normal fibroblast cell. As a result, cell proliferation was inhibited after the treatment (Fig. 2), and the proportion of SA-β-gal positive cells, a kind of senescence cell marker, was increased. Cellular senescence was similarly induced when only calcium was pumped into the cells without causing plasma membrane damage, indicating that an elevated intracellular calcium level, plays an important role in cellular senescence.

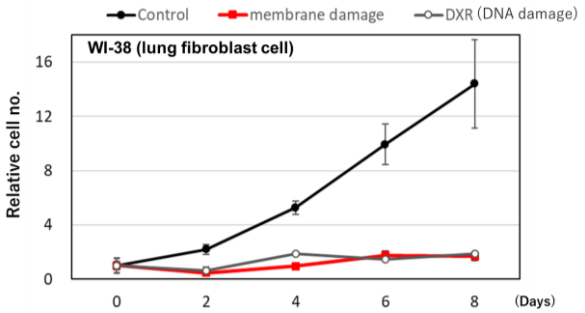

Figure2 Transient plasma membrane damage inducing treatment showed cell cycle arrest.

I tried to find key phenomena for the cell cycle arrest after the plasma membrane damage repair and found that mitochondria (energy factory of the cell) showed rapid fragmentation (fig.3).

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In addition to mitochondrial morphology, plasma membrane damage or calcium influx caused many changes in mitochondrial function and gene expression from the genome. I'm conducting a specio-temporal and multiomics analyses of changes in gene transcription and protein expression/localization related to cellular senescence by RNA-seq, proteomics, and microscopic observation.

The purpose of these analyses is to identify the mechanism leading to cellular senescence induced by the plasma membrane damage and to search for cellular senescence markers specific to the plasma membrane damage. In the future, I would like to develop this research into the suppression of senescence/aging.

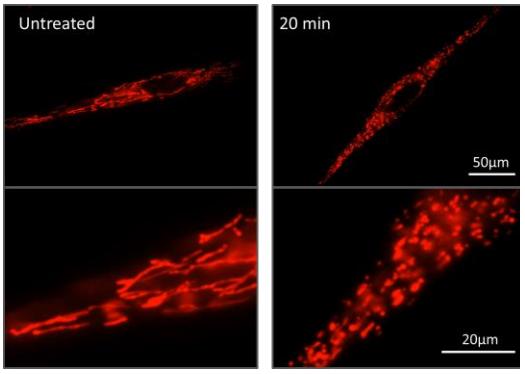

Figure3 Rapid mitochondrial fragmentation was observed shortly after the membrane damage introducing treatment.

3 Collaborations

Keiko Kono, Yatzu Chiu, Nurhanani Binti Razali, Kojiro Suda (Kono Unit, OIST)
Naoki Urakawa, Satoru Nakamura, Mariko Kishimoto (Nagoya University)
Shigeyuki Kawano (Future Center Initiative, The University of Tokyo)
Tetsuya Higashiyama (University of Tokyo)
Narie Sasaki (Ochanomizu University)

4 Publications and other output

One publication, one paper in revision, four in the pipeline

[Publication]

Urakawa N, Nakamura S, Kishimoto M, Moriyama Y, Kawano S, Higashiyama T, Sasaki N. Semi-in vitro detection of Mg2+-dependent DNase that specifically digest mitochondrial nucleoids in the zygote of *Physarum polycephalum*.
Sci Rep 2022 Feb 22;12(1):2995. doi: 10.1038/s41598-022-06920-2. PMID: 35194142

Two co-author of the presentations at the conference

Nurhanani Razali, Yohsuke Moriyama, Yatzu Chiu and Keiko Kono
Plasma membrane damage induces wound-healing SASPs in normal human fibroblasts
The 6th International Cell Senescence Association Conference (2021-11-19)

Yatzu Chiu, Yohsuke Moriyama, Nurhanani Binti Razali and Keiko Kono
The miRNA Signature Associated with Plasma Membrane Damage-dependent Senescence
The 6th International Cell Senescence Association Conference (2021-11-19)

STG representative (2022.01-)
Female faculty recruiting working group (2022.03-)
Vice mentor of rotation student: Tara Turkki
Mentor of Okinawa science mentoring program (2021 summer)
Talk at RAM2021 (Researchers appreciation month)