【Grant-in-Aid for Scientific Research (S)】

**Broad Section G**

# Title of Project : Elucidation of prevalent molecular mechanisms for cell competition

FUJITA Yasuyuki
(Kyoto University, Graduate School of Medicine, Professor)

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## 【Purpose and Background of the Research】

In the multi-cellular community, cells with different properties often compete with each other for survival and space. This process is named cell competition. Using originally established mammalian cell culture systems and mouse model systems, Principal Investigator Fujita has revealed that cell competition can occur between normal and transformed epithelial cells in mammals for the first time worldwide. For example, when oncoprotein Ras-transformed cells are surrounded by normal epithelial cells, the transformed cells become loser of cell competition against normal cells and are eventually eliminated into the apical lumen of epithelia. This result implies a novel concept that normal epithelial cells are able to sense the neighboring 'aberrant' cells and actively eliminate them from epithelial tissues.

In this study, we are addressing the two essential questions that remain to be answered in the field of cell competition.

i) Upon cell competition, how do winner and loser cells sense the differences from each other?

ii) Are there any prevalent molecular mechanisms that regulate a variety of cell competition phenomena?

## 【Research Methods】

In this study, Principal Investigator Fujita and Co-Investigator Igaki will cooperatively perform screenings to identify regulatory molecules for cell competition using mammalian cell culture systems and *Drosophila in vivo* systems, respectively. The ultimate goal is to elucidate prevalent molecular mechanisms of cell competition that are evolutionarily conserved.

1) Identification of regulatory proteins for cell competition using mammalian cell cultures (Fujita): Fujita will extensively identify cell competition regulators using two screening approaches: i) phage-antibody display screening targeting the extracellular domain of membrane proteins, ii) Translating Ribosome Affinity Purification (TRAP) targeting newly synthesized mRNA in ribosomes.

2) Identification of regulatory proteins for cell competition using *Drosophila* (Igaki): Large-scale fly genetic screenings will be performed to extensively identify genes regulating cell competition. The functional role of the identified molecules will be examined using two *Drosophila* cell competition experimental systems. In addition, the role of mammalian homologue in cell competition will be also examined using Fujita's mammalian experimental systems. Conversely, fly homologues of the identified molecules in mammalian systems will be examined in two *Drosophila* cell competition systems.

3) Functional analyses of identified molecules using *in vitro*, *ex vivo* and *in vivo* systems (Fujita, Igaki): The functional role of molecules identified by screenings will be analysed *in vitro*, *ex vivo* and *in vivo*. For *ex vivo* and *in vivo* analyses in mammals, cell competition mouse model systems will be used, which was originally established by Fujita's group. Organoid cultures and immunocytochemistry for various epithelial tissues such as pancreas, lung, mammary glands and guts will be used for analyses.

## 【Expected Research Achievements and Scientific Significance】

Once prevalent cell competition marker proteins are identified, it will become possible to capture various cellular processes or phenomena that involve cell competition, which will lead to elucidation of novel biological phenomena or application to various research fields.

## 【Publications Relevant to the Project】

- Kon, S., Ishibashi, K., Katoh, H., Kitamoto, S., Shirai, T., Tanaka, S., Kajita, M., Ishikawa, S., Yamauchi, H., Yako, Y., Kamasaki, T., Matsumoto, T., Watanabe, H., Egami, R., Sasaki, A., Nishikawa, A., Kameda, I., Maruyama, T., Narumi, R., Morita, T., Sasaki, Y., Enoki, R., Honma, S., Imamura, H., Oshima, M., Soga, T., Miyazaki, J., Duchen, M. R., Nam, J.-M., Onodera, Y., Yoshioka, S., Kikuta, J., Ishii, M., Imajo, M., Nishida, E., Fujioka, Y., Ohba, Y., Sato, T., and Fujita, Y. Cell competition with normal epithelial cells promotes apical extrusion of transformed cells through metabolic changes. Nature Cell Biology, 19(5):530-541 (2017).
- Hogan, C., Dupré-Crochet, S., Norman, M., Kajita, M., Zimmermann, C., Pelling, A.E., Piddini, E., Baena-López, L.A., Vincent, J. P., Hosoya, H., Itoh, Y., Pichaud, F. and Fujita, Y. Characterization of the interface between normal and transformed epithelial cells. Nature Cell Biology, 11 (4), 460-467 (2009).

## 【Homepage Address and Other Contact Information】

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