

Results report

1. Title of Research and Development :

Preemptive cancer treatments based on detection and elimination of precancerous cells using cell competition and supercompetition markers

2. Principal Investigator : **Yasuyuki Fujita** (Professor at Institute for Genetic Medicine, Hokkaido University)

3. Counterpart Principal investigator : **Eduardo Moreno** (Professor at Department of Institute of Cell Biology, Bern University)

4. Results of Research and Development:

The aim of this research project is to establish a novel and innovative cancer preventive medicine by studying cell competition between normal and transformed epithelial cells in a comprehensive manner through close collaborations between Japanese and Swiss groups. In this year, we have obtained the following outcomes.

1) By using various approaches, we have explored molecular mechanisms whereby cell competition between normal and transformed epithelial cells are regulated. Especially, by using a variety of biochemical cell fractionation methods and quantitative mass-spectrometry (SILAC), we have successfully identified multiple (potential) cell competition regulators.

In particular, we have found that mitochondrial activity is substantially decreased in RasV12-transformed cells when they are surrounded by normal epithelial cells. Increased expression of PDKs is responsible for the down-regulation of mitochondrial activity. Addition of DCA (Dichloroacetate), an inhibitor of PDKs, significantly suppresses the apical extrusion of RasV12-transformed cells, suggesting that PDK-mediated mitochondrial down-regulation plays a positive role in the elimination of transformed cells. Furthermore, expression of LDH is enhanced in RasV12-transformed cells surrounded by normal cells, and suppression of LDH activity leads to formation of basal protrusions. These data suggest that the Warburg effect-like phenotype can occur at the initial stage of carcinogenesis, which plays a tumor-suppressive role by promoting elimination of transformed cells from epithelial tissues. By further developing this new research field, we would create a novel type of cancer treatment: eradication of transformed cells by enhancing a defensive force of neighbouring normal epithelial cells.

2) In June, 2015, one PhD student in Fujita lab stayed at Dr. Moreno's lab for one month and acquired the technique of *Drosophila* genetics. In addition, Prof. Fujita (PI in the Japanese side) also visited Dr. Moreno's lab, and intensive discussion was held between the two groups as to the mutual research progress and upcoming collaborations. Thus, since the start of this collaborative project, close interactions and mutual exchange of young scientists have been promoted, which profoundly help them equip international sense.