



第 601 回 難研セミナー
第 174 回 難治疾患共同研究拠点セミナー
(お茶の水ニューロサイエンスセミナー共催)

Role of WW domain-containing proteins in mechanotransduction, Golabi-Ito-Hall syndrome and Ebola virus egress

演者

Prof. Marius Sudol (シンガポール国立大学)

日時

2019 年 7 月 16 日 (火) 16:00 - 17:00

会場

M&D タワー9 階 大学院講義室 4

講演要旨

Research in my new laboratory is focused on molecular functions of 3 WW domaincontaining proteins. We investigate the role of YAP proto-oncogene as a mechanosensor and the mechanism by which a mutation within WW domain of PQBP1 gene causes Golabi-Ito Hall syndrome. We also we study the role of WW domain of E3 ubiquitin ligases in Ebola virus (EV) budding. A physical stretching of a monolayer of various cells results in a fast translocation of YAP effector from the cytoplasm to the cell nucleus. In MKN 28 cells, within 3 minutes after stretching the majority of YAP protein is found in cell nuclei. The fast translocation of YAP is not dependent on transcription. We generated YAP deficient cells using CRISPR/Cas9 method. In two cells lines (MKN28 and EpH4) YAP-minus cells are 5x more rigid, compared to controls. Collectively our mechanical, biochemical and genetic approaches are aimed at the molecular description of the Hippo-YAP pathway and how it senses changes in the physical environment. We hope to uncover new modalities to control the loss of cell contact inhibition in cancer. A point mutation in the WW domain of a brain factor that regulates mRNA splicing, PQBP1 gene, is a loss of function mutation that abrogates PQBP1 protein complexes with RNA splicing factors. This mutation (Y to C) causes Golabi-Ito-Hall (GIH) syndrome of intellectual disability. The GIH mouse was generated. The main aim of this project is to perform RNAseq on brains of GIH and wild type mice to delineate transcripts that are abnormally spliced. Our ultimate aim is to correct this genetic lesion by using CRISPR/Cas9 gene editing. We showed that WW domains of E3 ubiquitin ligases are critical for budding of several viruses including EV. We decided to screen FDA approved drugs for the inhibitory activity against EV. We do have two successes, one of which is an FDA approved drug that inhibited cellular E3 ligase and viral VP40-protein interaction.

多数の皆様のお来聴をお願い申し上げます。

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