Chromosome 8p engineering reveals increased metastatic potential targetable by patient-specific synthetic lethality in liver cancer

Huth, T., Dreher, E. C., Lemke, S., Fritzsche, S., Sugiyanto, R. N., Castven, D., ... & Roessler, S. *Science Advances, 9*(51), eadh1442.(2023)

Presenter: Mei Xuan Ooi **Date/Time:** 2024/02/29, 15:10 – 16:00

Commentator: Professor Chung-Liang Ho **Location:** Medical Building Classroom 601

Background: Chromosomal alterations, genomic instability, and aneuploidy are a hallmark of cancer. Up to 88% of human cancers harbor arm-level chromosomal alterations which affect one-fourth of their whole genome. In hepatocellular carcinoma, a median of eight chromosome arm-level aneuploidies is detected per tumor. Among those arm-level alterations, chromosome 8p (chr8p) loss of heterozygosity (LOH) is one of the most frequent deletions in solid tumors. Clinical studies have shown that increased occurrence of metastasis in patients with chr8p LOH. However, the underlying mechanisms remain poorly understood.

Objective/Hypothesis: To investigate how heterozygous loss of chr8p affects cancer progression and to identify potential targets specific for patients harboring this chromosomal alteration.

Results: Firstly, they found that chr8pOH may be selected by cumulative haploinsufficiency of multiple tumor suppressive genes accounting for poor overall patient survival. They engineered liver cancer cell lines with heterozygous loss of chr8p to study the effects of potential cumulative haploinsufficiency on chr8p. Next, their RNA-seq results suggested that heterozygous loss of chr8p alters genome-wide RNA expression and affects metastasis-associated pathways. To elucidate how chr8p loss increases metastatic potential and to identify potential metastasis suppressor genes on chr8p, they conducted RNA interference (RNAi) screening of heterozygous loss of chr8p and the results suggested a metastatic phenotype in vitro. Genome-wide CRISPR-Cas9 knockout screening was performed and Nudix-type motif 17 (NUDT17) was identified as one of the top candidates of chr8p-dependent vulnerabilities. Their thorough study then revealed that NUDT18, a paralog to NUDT17 was associated with chr8p. Both NUDT17 and NUDT18 are synthetic lethal paralogs in liver cancer and affect ROS response.

Conclusion: Genome-wide CRISPR-Cas9 viability screening in isogenic chr8p-deleted cells demonstrated previously unidentified synthetic lethal targets and vulnerabilities accompanying by chr8p deletion. Chr8p deletion sensitizes tumor cells to targeting the reactive oxygen sanitizing enzyme NUDT17. Thus, chromosomal engineering led to the identification of previously unidentified synthetic lethalities specific to chr8pLOH.