加齢研セミナー

日　時: 平成30年4月3日(火)午後4時～6時
Tuesday, 3 April 2018, 16:00～18:00

場　所: 加齢研実験研究棟7階　セミナー室1
7th Floor, Seminar Room 1,IDAC Center for Basic Aging Research

講　師: 1. 16:00-17:00 Carlos Carmona-Fontaine
2. 17:00-18:00 Thales Papagiannakopoulos

所　属: 1. Center for Genomics and Systems Biology, New York University
2. Department of Pathology, New York University Medical School

演　題: 1. The role of extracellular metabolites in cancer
2. Uncovering metabolic bottlenecks in lung cancer

担　当: 本橋 ほづみ(所属　遺伝子発現制御分野・内線8550)
Hozumi Motohashi (Dept. Gene Expression Regulation・ext8550)

要　旨:

1. The Allee effect, named in honor of ecologist W. Allee, is a cornerstone in evolutionary theory that explains why in cooperative societies individual fitness depends on the population size. This key concept has been theorized to be important in cancer but we lack empirical models. Using our expertise in quantitative experiments and mathematical modeling we developed a new system where we show that cancer cells need to cooperate in order to survive and grow under nutrient scarcity. A central observation in our data is that sparse tumor cells populations are more susceptible to nutrient starvation and will go extinct unless they reach critical density levels. We unveil a novel cooperative mechanism by which cells collectively digest extracellular peptides generating free amino acids that accumulate outside cells and become a shared resource. Consistent with the Allee effect, this collective strategy is only effective when cell density is high because low density populations die before accumulating meaningful levels of free amino acids. We determined that this digestion is mediated by membrane-bound aminopeptidases and meta-analysis of TCGA data reveals that this enzyme family is upregulated across virtually all cancers. We propose that the sharing of metabolic resources is a wide spread, growth-factor independent, form of cell cooperation and that it is key to our understanding of tumor growth and malignancy.

2. Cancer is a multistep process that involves alterations in cell autonomous and non-cell autonomous events that are modulated by metabolic factors. During tumorigenesis cancer cells continuously encounter metabolic bottlenecks as a result of accelerated growth, overall increased metabolic demand and increased oxidative stress due to the formation of reactive oxygen species. Our laboratory investigates how genetic alterations in metabolic pathways, which are mutated in a large subset of lung cancers, promote tumor initiation and progression by rewiring cell autonomous and non-cell autonomous metabolic pathways and enable cancer cells to overcome metabolic bottlenecks. We use a combination of genetically-engineered mouse models, an accelerated CRISPR/Cas9-based experimental platform and biochemical approaches to identify metabolic liabilities that can be exploited using novel targeted therapies.
Our studies focus on elucidating the cell autonomous and non-cell autonomous mechanisms underlying novel metabolic dependencies in KEAP1 mutant tumors and explore the therapeutic potential of targeting metabolism in highly relevant pre-clinical mouse and human lung cancer models. Finally, we determine the broader implications of our findings in other cancer types with genetic, epigenetic or post-transcriptional alterations in the KEAP1/NRF2 pathway.

主催／加齢医学研究所研究会同窓会