National Cancer Centre Singapore
SingHealth

DEC 11th

Induction of an Epigenetic Field Involving Epithelial and Stromal Cells by Chronic Inflammation

Time:

Monday
2.00pm – 3.00pm



Toshikazu Ushijima, M.D., Ph.D.

Chief, Division of Epigenomics
National Cancer Center Research Institute
Tokyo, Japan

Venue:

Duke-NUS
Meeting Rm
7C
Level 7

Abstract

Epigenetic alterations can be a driver of various diseases, including cancer. Notably, aberrant DNA methylation is present in normal-appearing tissues long before cancer develops, and its level is correlated with cancer risk [Maekita, Clin Cancer Res, 12:989, 2006]. Etiologically, exposure to chronic inflammation is a potent inducer of aberrant DNA methylation in gastric tissues [Niwa, Cancer Res, 70:1430, 2010]. Inflammation capable of inducing aberrant methylation is consistently associated with increased expression of *Il1b*, *Tnfa*, and *Nos* [Katsurano, Oncogene, 31:342, 2012].

Mechanistically, gastric tissues exposed to chronic inflammation or cells treated with IL1b did not have increased DNMT expression. However, treatment of cells with nitric oxide up-regulated DNMT enzymatic activity. At the same time, inflammation-exposed gastric tissues had increased expression of *Tet*-targeting miRNAs, such as *miR-26b*, via NF-kB activation, decreased expression of three *Tet* genes, and decreased hmC contents. These strongly indicated that activated offence and weakened defense are important for DNA methylation induction [Takeshima, in preparation].

In addition to epithelial cells, we revealed that stromal cells can harbor epigenetic alterations. Again, chronic inflammation was suggested to induce epigenetic alterations in fibroblasts. Moreover, fibroblasts in cancer tissues, which are known to promote cancer cell aggressiveness, had epigenetic reprogramming due to alterations in DNA methylation and H3K27me3, some of which caused increased secretion of growth signal molecules [Maeda, in preparation].

Clinically, by a multicenter prospective cohort study involving 826 patients for 5.46 years, we demonstrated that people with high levels of aberrant DNA methylation in normal gastric tissues have a much higher risk of gastric cancer [Maeda, Gut, 66:1721, 2017]. Now, the epigenetic field involving epithelial and stromal cells offers a powerful tool for cancer risk diagnosis and novel targets for cancer prevention and therapy.

Hosted by:

Professor
TEH Bin Tean

About the Speaker

Dr. Toshikazu Ushijima is the Chief of Division of Epigenomics, National Cancer Center Research Institute (NCCRI), Tokyo. He graduated from the University of Tokyo School of Medicine in 1986, and started basic research in 1989. He developed one of the first genome-wide screening techniques for changes in DNA methylation. He established the concept of epigenetic field cancerization, showed that inflammation is critical for its formation, and clinically demonstrated that the degree of a field can be used for precision cancer risk diagnosis. He also identified the CIMP in neuroblastomas, and showed that it is strongly associated with poor prognosis. He is serving as an Associate/Senior Editor for Cancer Research, Cancer Letters, Gastric Cancer, and Cancer Science, and as an editorial board member for many journals. He has received Incitement (1997) and Mauvernay (2009) awards of JCA, President award of NCC (2012), the Tahara award of the Japanese Gastroenterological Carcinogenesis Society (2012), and the Uehara *Helicobacter* award of the Japanese *Helicobacter* Society (2013).

All are welcome, no registration required