D5 Medical & Life Science Seminar (Elective 2 credits)

Academic Year 2018 **"International Biomedical Research Seminars"**

Insights into the Function of SETD2 and H3K36 Trimethylation in Leukemia, Chemo-resistance and Hematopoietic Stem Cells

Speaker: **Gang Huang Ph.D.**

Associate Professor, Division of Pathology,
Cincinnati Children's Hospital Medical Center, USA,
Visiting Professor, IRCMS

Date: **November 21, 2018 (Wednesday)**

Time: 17:30 –

Venue: IRCMS 1F Meeting Lounge

Abstract

The SET domain containing 2 (*SETD2*) gene encodes the histone 3 lysine 36 (H3K36) methyltransferase which is responsible for tri-methylation (H3K36me3). Previously, we identified *SETD2* loss-of-function mutations in 22% of MLL-rearranged acute leukemia, implicating a mechanism for cooperativity between *SETD2* mutations and MLL fusions. Indeed, we found a global crosstalk between the oncogenic DOT1L-H3K79me2 axis and the tumor suppressive SETD2-H3K36me3 axis in gene regulation. Moreover, recurrence of cooperative mutations in *SETD2* is enriched in refractory/relapsed leukemia. We generated two novel loss-of-function Setd2 mutation alleles, both of them cooperate with MLL-AF9 to accelerate leukemia development. Importantly AML with Setd2 mutation allele results in resistance to standard chemo treatment by altered cell-cycle checkpoints. Checkpoint inhibition by either CHK1 or WEE1 inhibitor could re-sensitize resistant AML cells to chemo-therapy. Thus, exploring this tumor vulnerability with synthetic lethal approach could be an effective therapeutic strategy to overcome chemo-resistant. Last, Setd2 knockout in the adult hematopoiesis results in leukopenia, anemia, increased platelet, and erythroid dysplasia in bone marrow. Setd2 knockout hematopoietic stem cells lose quiescence and self-renewal, but increase differentiation and apoptosis. Mechanistically, we found a critical role of Setd2 in maintaining the fitness of HSCs and adult hematopoiesis through restricting transcriptional elongation of RNA polymerase II.

◆Essay / To IRCMS: ircms@jimu.kumamoto-u.ac.jp
Cc: Student Affairs Sec. : iyg-igaku-3@jimu.kumamoto-u.ac.jp

IRCMS **International Research Center for Medical Sciences (IRCMS)**

TEL:096-373-6847 FAX:096-373-6869 ircms@jimu.kumamoto-u.ac.jp