Cellular Memory Laboratory
Chief Scientist: Yoichi Shinkai (Ph.D.)

(0) Research field

CPR Subcommittee: Biology

Keywords: epigenetics, transcriptional regulation, protein and DNA methylation, retrotransposons

(1) Long-term goal of laboratory and research background

Our laboratory's principal objective is to understand the molecular mechanism of epigenetic gene regulation and the role of epigenetics in health and disease. To address these topics, we take multidisciplinary approaches, including molecular biology, biochemistry, cell biology, structural biology and mouse molecular genetics.

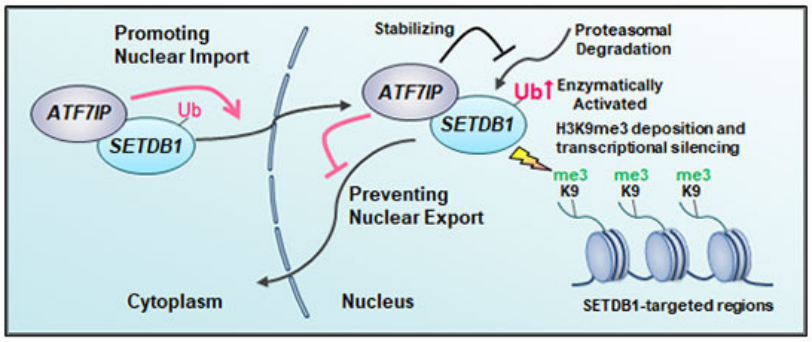
(2) Current research activities (FY2019) and plan (until Mar. 2025)

G9a-dependent histone methylation can be induced in G1 phase of cell cycle. Fukuda M. Sakaue-Sawano A. Shimura C. Tachibana M. Miyawaki A. Shinkai Y*. ***Sci Rep.*** 9:956. (2019)

In collaboration with Atsushi Miyawaki's lab in CBS, we demonstrated that the histone methyltransferase G9a can methylate histone H3 lysine 9 (H3K9) in G1 phase of cell cycle. Using cell cycle-specific degrons, we achieved G1 or late G1-to M phases specific accumulation of exogenous G9a in G9a deficient cells. Importantly, global levels of H3K9me2 were significantly recovered by both cell types. These data indicate that H3K9me2 may be plastic and inducible, even in the long-living, terminally-differentiated, post-mitotic, G0-G1 cell population *in vivo*. This knowledge is valuable in designing epigenome-manipulation-based treatments for diseases (1).

ATF7IP regulates SETDB1 nuclear localization and increases its ubiquitination. Tsusaka T. Shimura C. Shinkai Y*. ***EMBO Rep.*** 20:e48297. (2019)

The lysine methyltransferase, SETDB1, is one of the enzymes responsible for the methylation of histone H3K9 and plays a key role in H3K9 trimethylation-mediated silencing of genes and retrotransposons. Here, we reported that how SETDB1's enzymatic activities can be regulated by the nuclear protein, ATF7IP, a known binding partner of SETDB1. Mechanistically, ATF7IP mediates SETDB1 retention inside the nucleus, presumably by inhibiting its nuclear export by binding to the N-terminal region of SETDB1, which harbors the nuclear export signal motifs, and also by promoting its nuclear import. The nuclear localization of SETDB1 increases its ubiquitinated, enzymatically more active form. Our results provided an insight as to how ATF7IP can regulate the histone methyltransferase activity of SETDB1 accompanied by its nuclear translocation. (Fig. 1) (4)。



F i g . 1 SETDB1 regulation mediated by ATF7IP

Research plan (until Mar. 2025): In my laboratory, we are challenging following three research topics, 1) biology of protein lysine methylation, 2) epigenetic silencing mechanisms mediated by H3K9 and DNA methylation, 3) epigenetic regulation

mechanism of higher-order biological activities and application to epigenome manipulation. Until the end of current mid-term plan (until Mar. 2025), we aim to complete the originally planned research for all three topics.

(3) Members as of March, 2020

(Chief Scientist)
Yoichi Shinkai
(Senior Research Scientist)
Tadahiro Shimazu, Akeo Shinkai
(Research Scientist)
Ayumi Yamada, Atsuko Shirai
(Special Postdoctoral Researcher)
Kei Fukuda
(Postdoctral Researcher)
Taiki Shimizu
(Technical Staff)
Kaoru Kotoshiba, Chikako Shimura, Kayako Nishimura
(International Program Associate)
Fang Qi
(Student Trainee)
Hiroaki Fujimoto, Kana Miyano
(Assistant)
Mika Ichihashi

(4) Representative research achievements

1. G9a-dependent histone methylation can be induced in G1 phase of cell cycle. Fukuda M. Sakaue-Sawano A. Shimura C. Tachibana M. Miyawaki A. Shinkai Y*. ***Sci Rep.*** 9:956. (2019).
2. Histone H3K9 Methyltransferase G9a in Oocytes Is Essential for Preimplantation Development but Dispensable for CG Methylation Protection. Yeung WKA, Brind'Amour J, Hatano Y, Yamagata K, Feil R, Matthew C. Lorincz MC, Tachibana M, Shinkai Y, Sasaki H*. ***Cell Rep.*** 27:282-293. (2019).
3. Histone H1 quantity determines the efficiency of chromatin condensation in both apoptotic and live cells. Kijima M. Yamagishi H. Hara Y. Kasai M. Takami Y. Takemura H. Miyanari Y. Shinkai Y. Mizuta R*. ***Biochem Biophys Res Commun.*** 512:202-207. (2019).
4. ATF7IP regulates SETDB1 nuclear localization and increases its ubiquitination. Tsusaka T. Shimura C. Shinkai Y*. ***EMBO Rep.*** 20:e48297. (2019).Fukuda M, Sakaue-Sawano A, Shimura C, Tachibana M, Miyawaki A, Shinkai Y.* G9a-dependent histone methylation can be induced in G1 phase of cell cycle. ***Sci Rep.*** 2019 9:956. doi: 10.1038/s41598-018-37507-5.

Supplementary

Laboratory Homepage
https://www.riken.jp/en/research/labs/chief/cell_mem/index.html
http://shinkai.riken.jp/index_en.html