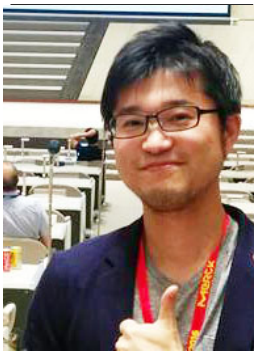
RNA Systems Biochemistry Laboratory (2020)
Chief Scientist: Shintaro Iwasaki (Ph.D.)



(0) Research field

CPR Subcommittee: Biology

Keywords:

Translation, RNA, translation inhibitor, RNA binding protein, next-generation sequencing

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

"The central dogma of molecular biology", which represents information flow from DNA to RNA to protein, has been a most basic principle in life. Recent quantitative and comprehensive analysis revealed that the amount of RNA could not simply correlate with protein abundance in cells, suggesting that "translation control" significantly contributes to gene expression more generally than as we previously expected. Our laboratory tackles to unveil the unknown mechanisms of translation control, by the combination of next-generation deep sequencing and classical biochemistry. Especially we harness a technique called ribosome profiling, which enables to measure cellular translation status in a genome-wide manner. Applying this technology to a variety of living organisms, we aim to reveal diverse biological phenomena controlled by protein synthesis regulations.

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

Molecular mechanism of anti-tumor translation inhibitor rocaglamide A

Tumor cells are often associated with increased protein synthesis. Thus, many translation inhibitors attract great interests because of the potency to tune the aberrant protein synthesis in tumor cells and thus suppress the cell growth. Rocaglamide A is a remarkable example of such a translation inhibitor. However, the molecular mechanism of the rocaglamide A still remains unclear. In addition to known target eIF4A (a translation initiation factor), we identified DDX3 as an alternative target of rocaglamide A (Representative research achievements 2). Given the dominant negative activity of the compound, our study revealed that the expression level of eIF4A and DDX3 is a determinant of rocaglamide A sensitivity in tumor cells.

Novel mode of action of splicing modulator spliceostatin A

Splicing modulator spliceostatin A has been known to possess a strong anti-tumor effect. However, the relation between splicing modulator compound and anti-cancer potential has remained enigmatic. We found that, other than splicing regulation, spliceostatin A leads to premature cleavage and polyadenylation of pre-mRNAs and long non-coding RNA MALAT1 (Representative research achievements 1).

Development of a technique to survey ribosome collisions

During decoding the codon, ribosome traverse along mRNAs is often impeded by various reasons. However, the identification where the ribosome halts the movement along mRNA has posed the analytic challenge. To solve this issue, we developed a novel technique called "disome profiling" (Representative research achievements 5). Since stalled ribosome may be collided with the trailing ribosome and form a unit of two ribosomes (disome), we collected the longer ribosome footprints originated from the disomes and analyzed them by next-generation deep sequencer. This approach allowed us to survey the ribosome collision sites in a genome-wide manner in a single codon resolution.

Future direction

We plan to apply these deep-sequencing-based technologies for various species and molecules and discover brand new biological phenomena associated by translation control. We also would like to develop novel methods that break through the barrier of sensitivity, resolution, and throughput of the pre-existing techniques.

(3) Members as of March, 2021

(Chief Scientist)
Shintaro Iwasaki

(Research scientist)
Eriko Matsuura

(Special Postdoctoral Researcher)
Yuichi Shichino

(Postdoctoral Researcher)
Haruna Yamashiro

(Technical Staff)
Mari Mito

(International Program Associate)
Chen Mingming
Apostolopoulos Antonios
Han Peixun

(Research Fellow)
Shiho Makino

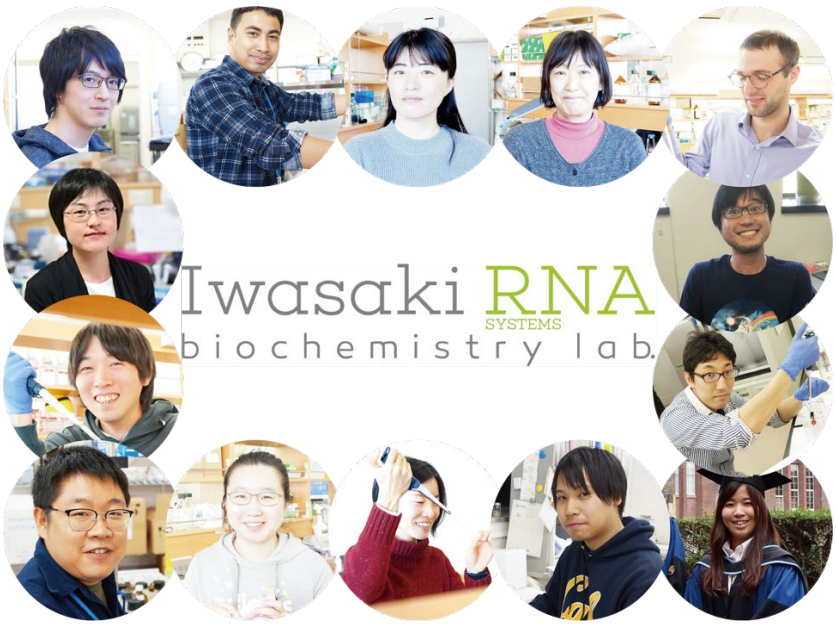
(Student Trainee)
Hironori Satito
Tomoya Fujita
Yusuke Kimura

(Assistant)
Rie Yokoyama

(4) Representative research achievements

1. "Yoshimoto R, Chhipi Shrestha JK, Schneider-Poetsch T, Furuno M, Burroughs MA, Noma S, Suzuki H, Hayashizaki Y, Mayeda A, Nakagawa S, Kaida D, **Iwasaki S***, and Yoshida M*. Spliceostatin A interaction with SF3B1 limits U1 snRNP availability and causes premature cleavage and polyadenylation. *Cell Chem Biol.* S2451-9456(21)00111-2. (2021) DOI: 10.1016/j.chembiol.2021.03.002
2. Chen M, Asanuma M#, Takahashi M#, Shichino Y, Mito M, Fujiwara K, Saito H, Floor SN, Ingolia NT, Sodeoka M, Dodo K, Ito T, and **Iwasaki S***. Dual targeting of DDX3 and eIF4A by the translation inhibitor rocaglamide A. *Cell Chem Biol.* 28(4):475-486.e8. (2021) DOI: 10.1016/j.chembiol.2020.11.008 (#: equal contribution)
3. Suzuki Ta, Yashiro Y, Kikuchi I, Ishigami Y, Saito H, Matsuzawa I, Okada S, Mito M, **Iwasaki S**, Ma D, Zhao X, Asano K, Lin H, Kirino Y, Sakaguchi Y, and Suzuki Ts. Complete chemical structures of human mitochondrial tRNAs. *Nat Commun.* 11(1):4269. (2020) DOI: 10.1038/s41467-020-18068-6
4. Nakazawa K, Shichino Y, **Iwasaki S**, and Shiina N. Implications of RNG140 (caprin2)-mediated translational regulation in eye lens differentiation. *J Biol Chem.* 295(44):15029-15044. (2020) DOI: 10.1074/jbc.RA120.012715
5. Han P, Shichino Y, Schneider-Poetsch T, Mito M, Hashimoto S, Udagawa T, Kohno K, Yoshida M, Mishima Y, Inada T, and **Iwasaki S***. Genome-wide survey of ribosome collision. *Cell Rep.* 31(5):107610. (2020) DOI: 10.1016/j.celrep.2020.107610

Supplementary



Laboratory Homepage
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