RNA Systems Biochemistry Laboratory
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 (FY2021) and plan (until Mar. 2025)

Discovery of autophagy-mediated RNA decay mechanism

Autophagy has been recognized as a mechanism to degrade proteins and organelles selectively or non-selectively. Although the potency of autophagic decay of nucleic acid RNA has been suggested, the details have long remained elusive. In yeast, we surveyed the mRNA degraded by autophagy pathways and found that the mechanism is elicited in an mRNA-selective manner (Representative research achievements 5). This selectivity is associated with ribosome loading on the mRNAs. We also showed that Atg24/Atg20/Snx41 complex is a key regulator for this process.

Translation modulation pathway elicited by spliceostatin A

Splicing modulator spliceostatin A has been known to possess an anti-tumor effect. However, the relation between splicing modulator compounds and anti-cancer potential has remained enigmatic. We found that spliceostatin A, a splicing modulator, leads to widespread translation from introns. The aberrant protein product shows the condensation-prone feature, evokes the proteotoxic response, and then suppresses the global translation (Representative research achievements 4).

Inhibitor of the integrated stress response

A variety of stresses, such as ER stress, viral infection, and amino acid/heme depletion, leads to a common response, so-called integrated stress response (ISR). ISR shuts off the global translation and increases the protein synthesis from a subset of mRNAs, to promote cellular recovery from the stresses. However, chronic ISR may be deleterious to such as neurons and cause diverse neurodegenerative diseases. Thus, potent ISR inhibitors attract huge interest due to their therapeutic potential. We found that NSs protein encoded in Sandfly fever Sicilian virus (SFSV) functions as an intense ISR inhibitor. We observed that translation re-programming by ISR is totally restored by NSs (Representative research achievements 3).

Future direction

We plan to apply these deep-sequencing-based technologies to various species and molecules and discover brand new biological phenomena associated with translation control. Given that organelle such as mitochondria and chloroplasts has a unique translation system than the cytosolic one, we would like to unveil the interconnection between organelle-cytosol protein synthesis. We also would like to develop novel methods that break through the barrier of sensitivity, resolution, and throughput of the pre-existing techniques.

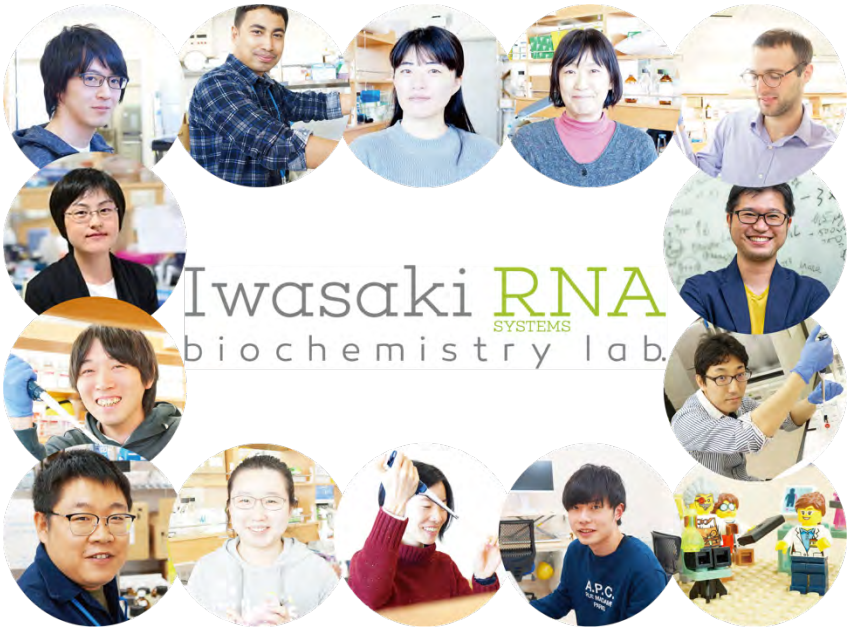
(3) Members as of March, 2022

(Chief Scientist)
Shintaro Iwasaki
(Research scientist)
Eriko Matsuura
(Special Postdoctoral Researcher)
Yuichi Shichino
(Postdoctoral Researcher)
Tomoya Fujita
(Technical Staff)
Mari Mito
(International Program Associate)
Chen Mingming
Apostolopoulos Antonios
Han Peixun
(Junior Research Associate)
Hironori Satito
(Research Fellow)
Shiho Makino
(Student Trainee)
Taisei Wakigawa
(Assistant)
Rie Yokoyama

(4) Representative research achievements

1. Kimura Y[#], Saito H[#], Osaki T, Ikegami Y, Wakigawa T, Ikeuchi Y, and **Iwasaki S***. Mito-FUNCAT-FACS reveals cellular heterogeneity in mitochondrial translation. *RNA.* 28(6):895-904. (2022) DOI: 10.1261/rna.079097.122 ([#]: equal contribution)
2. Fujita T, Yokoyama T, Shirouzu M, Taguchi H, Ito T, and **Iwasaki S***. The landscape of translational stall sites in bacteria revealed by monosome and disome profiling. *RNA.* 28(3):290-302. (2022) DOI: 10.1261/rna.078188.120
3. Kashiwagi K[#], Shichino Y[#], Osaki T[#], Sakamoto A, Nishimoto M, Takahashi M, Mito M, Weber F, Ikeuchi Y*, **Iwasaki S***, and Ito T*. eIF2B-capturing viral protein NSs suppresses the integrated stress response. *Nat Commun.* 12(1):7102. (2021) DOI: 10.1038/s41467-021-27337-x ([#]: equal contribution)
4. Chhipi Shrestha JK, Schneider-Poetsch T, Suzuki T, Mito M, Khan K, Dohmae N, **Iwasaki S***, and Yoshida M*. Splicing modulators elicit global translational repression by condensate-prone proteins translated from introns. *Cell Chem Biol.* 29(2):259-275.e10. (2022) DOI: 10.1016/j.chembiol.2021.07.015
5. Makino S, Kawamata T, **Iwasaki S***, and Ohsumi Y*. Selectivity of mRNA degradation by autophagy. *Nat Commun.* 12(1):2316. (2021). DOI: 10.1038/s41467-021-22574-6

Supplementary



Laboratory Homepage
https://www.riken.jp/en/research/labs/chief/rna_sys_biochem/index.html
http://iwasakirna.com/