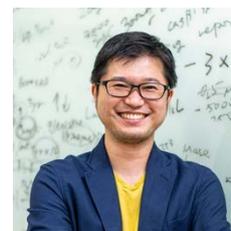


RNA Systems Biochemistry Laboratory
Chief Scientist: Shintaro Iwasaki (Ph.D.)



(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 we previously expected. Our laboratory tackles to unveil the unknown mechanisms of translation control, through the combination of next-generation deep sequencing and classical biochemistry. Especially we harness a technique called ribosome profiling, which enables us 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 (FY2022) and plan (until Mar. 2025)

Competition for survival between plants and fungi via translation inhibitors

In recent years, compounds called rocaglates have been attracting attention for their anticancer and antiviral (including the therapeutic effects against COVID-19) activities. Rocaglate is a secondary metabolite produced by *Aglaia*, a plant native to Southeast Asia, and inhibits translation by binding to eIF4A, a translation initiation factor. It was believed that *Aglaia* plant utilizes this translation inhibition by rocaglates for its own antifungal defense.

Contrary to the idea, we first discovered a new filamentous fungus (mold) that infects *Aglaia*. We named this filamentous fungus “*Ophiocordyceps* sp. BRM1 (strain BRM1)”. *De novo* transcriptome assembly identified unique amino acid substitution in eIF4 in the rocaglate binding pocket. We can recapitulate the rocaglate-resistance in the model fungi-plant infection system with genome-engineered *Colletotrichum orbiculare* onto cucumber. The study presented the evolution of fungi to adapt to rocaglate-synthesizing plants. This work was a wonderful collaboration with Shirasu lab from RIKEN CSRS and Ito lab from RIKEN BDR and was published in *eLife* (Chen *et al.* *eLife* 2023).

Function of post-translational modifications that occur on a ribosomal protein

Although it was previously thought that only a limited number of proteins undergo histidine methylation modification, recent comprehensive studies have shown that it occurs in a wider range of proteins than previously thought. There are two types of histidine methylation: π -N-position (π -N-methylhistidine or 1-methylhistidine) and τ -N-position (τ -N-methylhistidine or 3-methylhistidine). In particular, Hpm1 in yeast has been reported to be the only methyltransferase that methylates the τ -N position. A homolog of Hpm1, “METTL18,” is conserved in humans. However, the biological function of METTL18 and τ -N histidine methylation in humans has not been elucidated.

Harnessing propargylic *Se*-adenosyl-L-selenomethionine (ProSeAM), an analog of S-adenosyl-L-methionine (SAM), we surveyed the substrates of METTL18 *in vitro* and found that His245 of RPL3 (uL3) has τ -N-methylhistidine. CryoEM analysis of 60S ribosome revealed that this modification is stoichiometric in the complex. Ribosome profiling showed that methylated His245 is important for the slowdown of ribosome traversal on Tyr codon; otherwise, proteome integrity was abrogated probably due to the inefficiency of cotranslational protein folding. This work was a wonderful collaboration with Shinkai lab from RIKEN CPR, Sodeoka lab from RIKEN CPR/CSRS, and Ito lab from RIKEN BDR and was published in *eLife* (Matsuura-Suzuki *et al.* *eLife* 2022).

Future direction

Translation control is a rapid means to cope with environmental changes. Due to their sessile nature, plants may have a higher demand to use translational control. We are actively investigating borate-mediated translational regulation as a model.

(3) Members

as of March, 2023

(Chief Scientist)

Shintaro Iwasaki

(Research scientist / tenured)

Yuichi Shichino

(Postdoctoral Researcher)

Hiroataka To

(Technical Staff I)

Mari Mito

(International Program Associate)

Apostolopoulos Antonios

(Junior Research Associate)

Hironori Saito

(RIKEN Student Researcher M)

Kotaro Tomuro

(Student Trainee)

Han Peixun

Taisei Wakigawa

(Special Temporary Employee)

Rie Yokoyama

(Administrative Part-time Worker I)

Miho Tsunashima

(4) Representative research achievements (#: equal contribution, *: correspondence)

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4. Chhipi-Shrestha JK, Yoshida M*, and **Iwasaki S***. Filter trapping protocol to detect aggregated proteins in human cell lines. *STAR Protoc.* 3(3):101571. (2022) DOI: 10.1016/j.xpro.2022.101571
5. Shichino Y* and **Iwasaki S***. Compounds for selective translational inhibition. *Curr Opin Chem Biol.* 69:102158. (2022) DOI: 10.1016/j.cbpa.2022.102158

Supplementary



Laboratory Homepage

https://www.riken.jp/en/research/labs/chief/rna_sys_biochem/index.html

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