【Grant-in-Aid for Specially Promoted Research】

Molecular basis and physiological roles of various ribosome functions in gene regulation

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Project Information	Project Number : 25H00007　Project Period (FY) : 2025-2029 Keywords : Ribosome dynamics, Quality controls, Stress response, Metabolism, Neuron

Purpose and Background of the Research

●Outline of the Research

Regulation of translation rate is intricately linked to various cellular processes, including protein folding, localization to organelles, and mRNA stability—all of which contribute to the expression of functional proteins. Recent advances have revealed that ribosomes play roles beyond merely translating RNA; they are central to regulating the proteome. This study aims to uncover the hidden functions of ribosomes, explore the mechanisms behind their fate determination, and understand their physiological roles. By adopting a comprehensive approach that integrates genetics, biochemistry, structural biology, biophysics, and cell biology, we seek to elucidate the complex functions of ribosomes that go beyond their traditional role as simple translational machines.

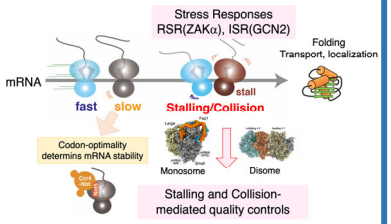


Figure 1. Research concept

●Background

It has become evident that ribosomes are not merely responsible for converting RNA into proteins—they are key regulators of the proteome. Abnormal ribosome dynamics can lead to faulty translation products, disrupting protein homeostasis. The Ribosome-Associated Quality Control (RQC) mechanism plays a critical role in maintaining protein homeostasis by rescuing the collided ribosomes caused by aberrant ribosome stalling and degrading defective proteins.

The collision sensor recognizes the distinct structure of colliding ribosomes and forms a K63-type polyubiquitin chain on the ribosomal protein uS10, leading to the RQT complex-mediated rescue of the collisions. The abnormal proteins on the 60S ribosomal subunit are targeted for ubiquitination and proteasomal degradation. Furthermore, a unique tag sequence is added to abnormal proteins by a primitive translation reaction that operates independently of mRNA, which plays a critical role in the degradation process.

The molecular mechanism behind the quality control of 18S NRD, which detects ribosome stagnation and triggers the degradation of the ribosome itself, has been further elucidated. The ribosome staling/collision activates Integrated Stress Response (ISR) and Ribotoxic Stress Response (RSR), highlighting the ribosome's essential role in sensing stress and eliciting cellular responses. Emerging evidence suggests that ribosomal functions may be specialized according to organ and cell type, further challenging the traditional view of ribosomes as mere translation machinery.

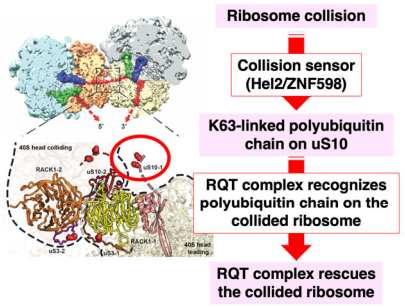


Figure 2. Mechanism of RQC

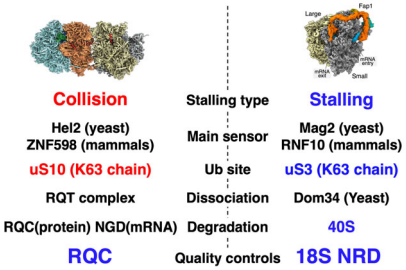


Figure 3. Quality controls for aberrant translation

●Questions and Purposes

The central question of this research focuses on the molecular basis of the ribosome's unknown regulatory functions and their physiological implications. Specifically, we seek to investigate the following questions: What mechanisms are involved in sensing abnormal ribosome speed? How does the cell determine the fate of stalled and colliding ribosomes (whether to maintain or resolve them)? What role does ribosome speed abnormality play in triggering stress responses? What molecular mechanisms govern the degradation of ribosomes due to speed abnormalities? How does tRNA selection occur within the context of the primordial translation system?

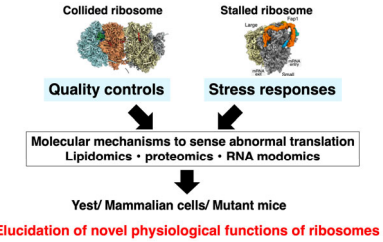


Figure 4. Aim of this research

Expected Research Achievements

Utilizing budding yeast, cultured cells, and individual mice, we aim to investigate the molecular mechanisms underlying ribosome function and its physiological consequences. Our research will focus on the following areas:

（1）Molecular Mechanism and Physiological Function of quality controls that recognize abnormal translation

We will examine how the ribosome collision sensor recognizes the specific structure of colliding ribosomes and ubiquitinates uS10, which is crucial for resolving ribosome collisions. We will also analyze the function of RQC in physiological aging and metabolism in various tissues and genetically modified mouse models.

（2）Protein Fate Determination via a Primitive mRNA-Independent Translation System

We will explore how a specific tag sequence (CAT tail) is added to abnormal proteins—a process conserved from prokaryotes to humans—through a translation mechanism independent of mRNA. Our analysis will focus on the molecular mechanisms involved in CAT tail formation and its impact on the fate of abnormal proteins, particularly concerning tRNA recognition. We will also assess its physiological implications in neuronal cells.

（3）Stress Response Induced by Ribosome Collision/Stall and Mechanisms of Ribosome Degradation

We will investigate how aberrant ribosome dynamics lead to cellular dysfunctions through the integrated stress response (ISR) and nucleic acid stress response (RSR). Our goal is to analyze the physiological significance of these responses and the mechanisms that regulate ribosome degradation due to abnormal translation.

（4）Mechanisms of translation rate- and ribosome collision-mediated mRNA Degradation

We will analyze the molecular mechanisms of translation rate-mediated mRNA degradation and No-Go Decay (NGD) quality control, a ribosome collision-mediated mRNA cleavage.

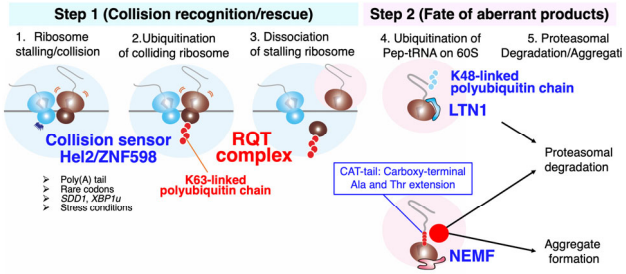
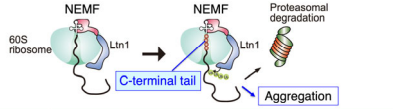


Figure 5. Mechanism of RQC



	Bacteria	Yeast	Mammals	
C-terminal tail	(Ala)n	(A/T)n	(A/T/G..)n	(Ala)n
Tailing factor	RqcH	Rqc2	NEMF	NEMF
Function/fate of products	Degradation tag for ClpXP protease	✓ Aggregation formation ✓ Ltn1-mediated ubiquitination	Aggregation formation	CRL2^{KLHDC10}/Pirh2-mediated ubiquitination(RQC-C)

Figure 6. Mechanism of CAT tail formation

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