【Grant-in-Aid for Transformative Research Areas（B）】

Translation and Reaction Sites: Toward Understanding Protein Society

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Purpose and Background of the Research

●Outline of the Research

Proteins, which are essential to life, undergo a series of processes before fulfilling their functions. Once mRNAs are translated into proteins, newly synthesized proteins go through multiple steps such as folding, protein assembly, transport, and localization to become functionally active (Figure 1A). However, do these steps truly occur sequentially and independently, as described in current textbooks? Recent studies suggest this may not be the case. For example, research groups led by Bernd Bukau and Günter Kramer reported that homodimer formation can occur co-translationally (Bertolini, Fenzl et al., 2021, Science), and Benoit Palancade's group demonstrated that components of the nuclear pore complex are translated near the nuclear envelope (Lautier, Penzo et al., 2021, Molecular Cell). Furthermore, unpublished data from Yuichi Shichino, a member in this research project, suggest that multiple processes—translation, protein assembly, and localization—occur simultaneously on lysosomes in a certain protein complex X (Figure 1B). Another member, Yoshitaka Matsuo, is investigating the ribosome biogenesis pathway, which involves a non-canonical flow: parts are translated in the cytoplasm, assembled into complexes in the nucleus, and finally become functional again in the cytoplasm (Figure 1C). These emerging findings collectively paint a picture in which the processes leading to protein functionality are flexibly optimized depending on the situation—much like human society. For instance, exporting a kimono woven in Japan to the U.S. makes sense, but delivering sushi made in Japan to be consumed in the U.S. is impractical. Similarly, some proteins can be translated anywhere in the cytoplasm and still be functional once transported to the lysosomes, while others require translation and protein assembly to be coupled on the lysosomes. In short, it is becoming clear that proteins do not follow the straightforward, textbook-like pathway (Figure 1A); instead, they seem to coordinate steps like production, modification, transport, reception, and consumption in a manner tailored to their function and cellular context—just as products in human society (Figure 1B,C).

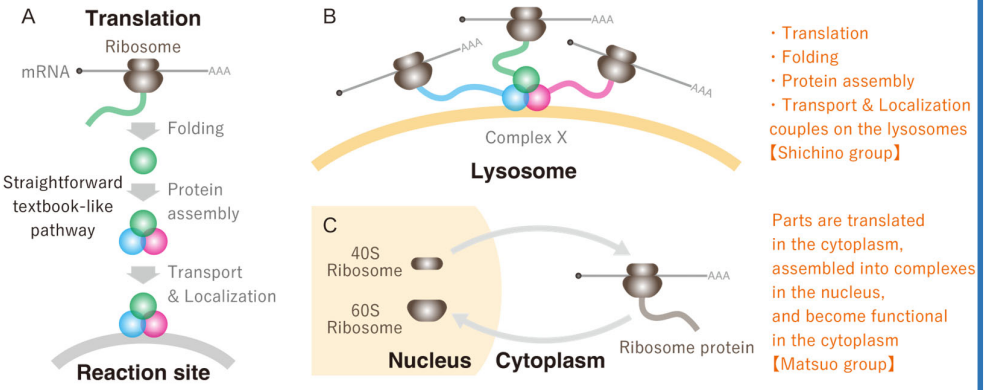

Figure 1. A new landscape of "translation" and "reaction sites" explored in this research project

Therefore, this research project focuses on both the starting point (translation) and the endpoint (reaction sites) of protein expression. By examining both ends of this journey, we aim to shed light on how the order and combination of elementary steps from translation to functionality are optimized on a case-by-case basis, much like human society. In doing so, we hope to uncover a novel societal view of proteins that transcends conventional frameworks.

Why, then, has research exploring the link between translation and reaction sites not been pursued until now? The main reason is the lack of appropriate technologies. Traditional in vitro biochemical methods, while powerful for dissecting individual molecular mechanisms, could not provide spatial information about where proteins are synthesized and function within cells. Recognizing this limitation, five researchers in this research project have each specialized in and refined techniques to bridge the gap between translation and reaction sites (Figure 2). By combining these complementary technologies, we aim to uncover a new, dynamic view of how proteins function in cells.

Expected Research Achievements

This research project aims to establish a new, non-canonical "societal view of proteins" by exploring the relationship between translation and reaction sites—a relationship that has remained largely unexamined until now. Through four integrated project components that combine the advanced technologies of each participating group (Figure 2), we aim to shed light on this unexplored landscape.

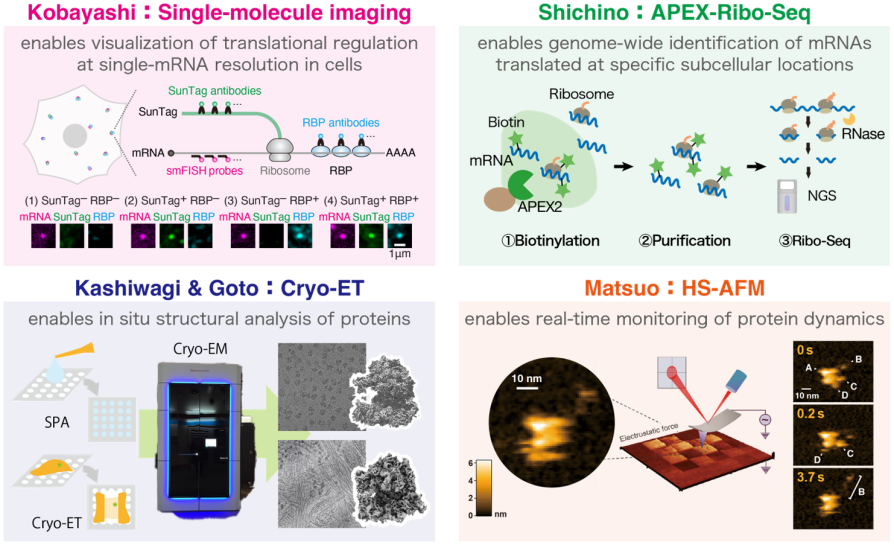

Figure 2. Four key technologies driving the exploration of "translation" and "reaction sites"

Specifically, we will investigate: (1) local translation, in which protein synthesis occurs in spatially confined reaction sites (**A01 Kobayashi group and A02 Shichino group**); (2) localized stress responses, in which translation is locally regulated in response to stress, leading to reorganization of reaction sites (**B01 Kashiwagi & Goto group**); and (3) ribosome biogenesis, in which components are translated in the cytoplasm, assembled into complexes in the nucleus, and then return to function in the cytoplasm—an example of "localized protein assembly" (**B02 Matsuo group**).

Homepage Address, etc.	Website of this research project : https://sites.google.com/view/translation-and-reaction-sites Website of Principal Investigator : https://sites.google.com/view/h-kobayashi-lab