NAIST® Research Highlights

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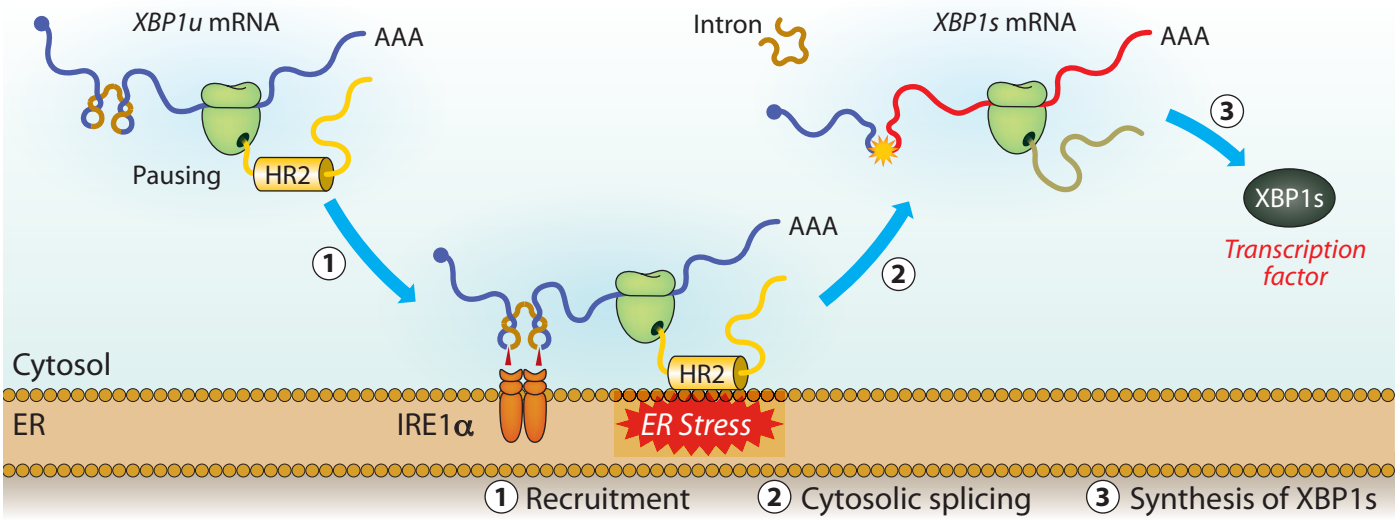

The NAIST team's proposed model for the action of XBP1u in translational pausing, mRNA splicing, and production of active XBP1s.

Molecular biology

Ribosome pause has critical role

A novel system in animal cells halts protein-synthesis to generate molecules that protect against disease

A little-known process in cell genetics — translational pausing — may be more important than previously thought. Scientists at NAIST have uncovered a new system that protects against the accumulation of misfolded proteins in a cellular compartment called the endoplasmic reticulum (ER). It may be involved in diabetes and neurodegenerative disorders.

Proteins, the building blocks of life, are assembled in a multi-stage process. First, the DNA code is 'transcribed' into a complementary molecule, messenger RNA (mRNA). This is then 'translated' into proteins at a structure called a ribosome. Normally, proteins are not functional until released from the ribosome. However, a team led by Kenji Kohno uncovered one — XBP1u — which plays a crucial role before it is even fully translated[1]. As XBP1u emerges from the ribosome, it drags the entire complex — ribosome, mRNA and protein — to the ER's external membrane. Here, a protein called IRE1α splices a section out of the *XBP1* mRNA (see figure). The modified mRNA translates into a new protein, XBP1s, which induces genes that prevent damaging misfolded proteins from accumulating in the ER.

> **"We want to know exactly how this translational pausing occurs and how translation is then restarted."**

Kohno's team identified a section of XBP1u, HR2, which causes the complex to attach to the ER membrane. Because HR2 lies close to the end of XBP1u, there is a risk that translation of XBP1u may be completed, and the protein released, before HR2 has had time to do its job. The scientists showed — by separating out the cell's proteins according to size and charge (a method called electrophoresis) — how this is prevented: another section of XBP1u causes translation to pause before XBP1u is complete.

This leaves the protein attached to the complex both during movement to the ER membrane and mRNA splicing. In sum, says Kohno, "Translational pausing of XBP1u enhances the distribution of its mRNA to the surface of the ER, which increases the efficiency of cytoplasmic splicing of XBP1u, producing a new mRNA encoding XBP1s."

Using mutants with reduced or extended translational pausing, the team showed the importance of the pausing process to both membrane targeting and efficient splicing of the mRNA. They also found that the pausing sequence continues to function when attached to other proteins, so could be used to study protein folding in general.

The easy availability of novel equipment and strong communication between laboratories has made this ground-breaking research possible. "Now," says Kohno, "we want to know exactly how this translational pausing occurs and how translation is then restarted."

Reference

1. Yanagitani, K., Kimata, Y., Kadokura, H. & Kohno, K. Translational pausing ensures membrane targeting and cytoplasmic splicing of XBP1u mRNA. *Science* **331,** 586-589 (2011).

More information about the group's research can be found at the Molecular and Cell Genetics webpage:
http://bsw3.naist.jp/eng/courses/courses207.html