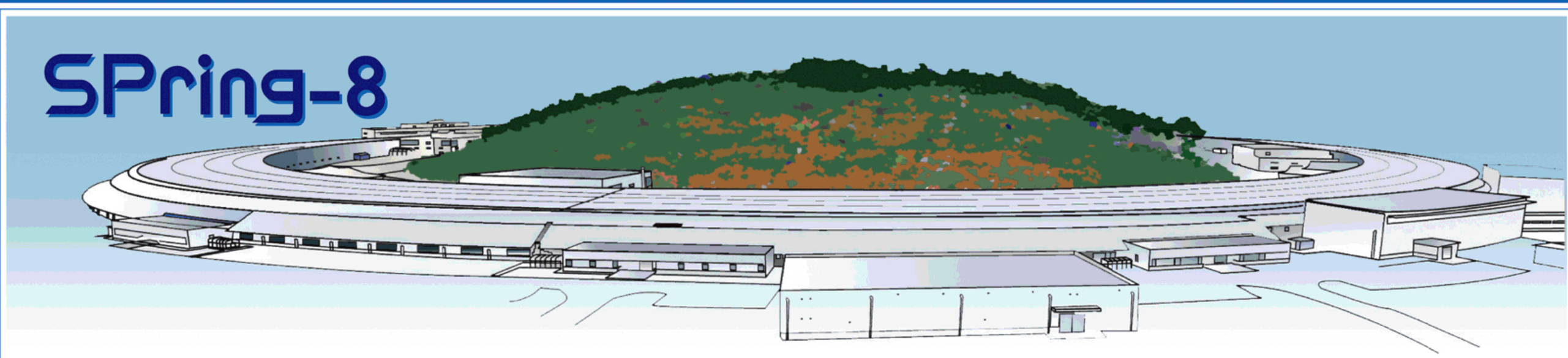
SPring-8



Elucidation of the Mechanism Creating the Small RNA that Inhibits Genome Mutation

The research group, at the University of Tokyo, Graduate School of Science, revealed a part of the molecular machinery in which a small RNA (ribonucleic acid)—responsible for protecting a genome (entire gene)—is created. The research was conducted as part of JST Mission-oriented Basic Research, and the group consisted of, among others, Prof. Osamu Nureki, Prof. Mikiko Shiomi, Assistant Prof. Hiroshi Nishimasu (special-appointment) and Hirotsugu Ishizu.

Animal genomes include a type of mobile gene, called a transposon, whose transfer in many cases is known to cause genome damage, inducing a variety of diseases. Living organisms have a built-in mechanism to regulate transposon expression and suppress transfer activity. In reproductive cells that are responsible for inheriting genetic information in an accurate fashion, a small RNA (piRNA) undertakes the role of protecting the genome from being damaged. Our basic understanding is that this RNA is composed of a long single-stranded RNA, but the mechanism by which it is created has been unknown.

The research group focused on the *Zucchini (Zuc) protein*, which is a class among the many proteins known to have a hand in piRNA production of drosophila and mice. Firstly, the crystal structure of Zuc protein was analyzed using the ultra-high intensity microbeam available at SPring-8 (BL32XU), which revealed that the protein has an optimized structure for slicing single-stranded RNAs. Subsequent biochemical analysis clearly indicated that the Zuc protein features enzyme activity capable of slicing a single-stranded RNA, supporting the results from X-ray crystal structure analysis. Additionally, cell biological analysis made it clear that the RNA slicing activity of the Zuc protein constitutes an integral part in producing piRNA and inhibiting transposon expression.

The true identity of the enzyme that slices a single-stranded RNA, required for producing piRNA, has long been in question, until this research indicated that the Zuc protein assumes the role. Experimental evidence obtained using drosophila and mice has proved that the mutation in the Zuc gene leads to infertility, and that animals (including humans) also possess Zuc proteins. Toward the future, the results of this research may hold significant promise for further elucidation of the pathogenic mechanisms of infertility in humans and animals.

The findings reported here were obtained through collaborative research with Prof. Haruhiko Shiomi (Keio University, School of Medicine) and Prof. Junken Aoki (Tohoku University, Graduate School of Pharmaceutical Science).

Reference: "Structure and function of Zucchini endoribonuclease in piRNA biogenesis"
Hiroshi Nishimasu, Hirotsugu Ishizu, Kuniaki Saito, Satoshi Fukuhara, Miharu K. Kamatani, Luc Bonnefond, Naoki Matsumoto, Tomohiro Nishizawa, Keita Nakanaga Junken Aoki, Ryuichiro Ishitani, Haruhiko Siomi, Mikiko C. Siomi & Osamu Nureki
Nature **491** , 284-287 published online 14 October 2012

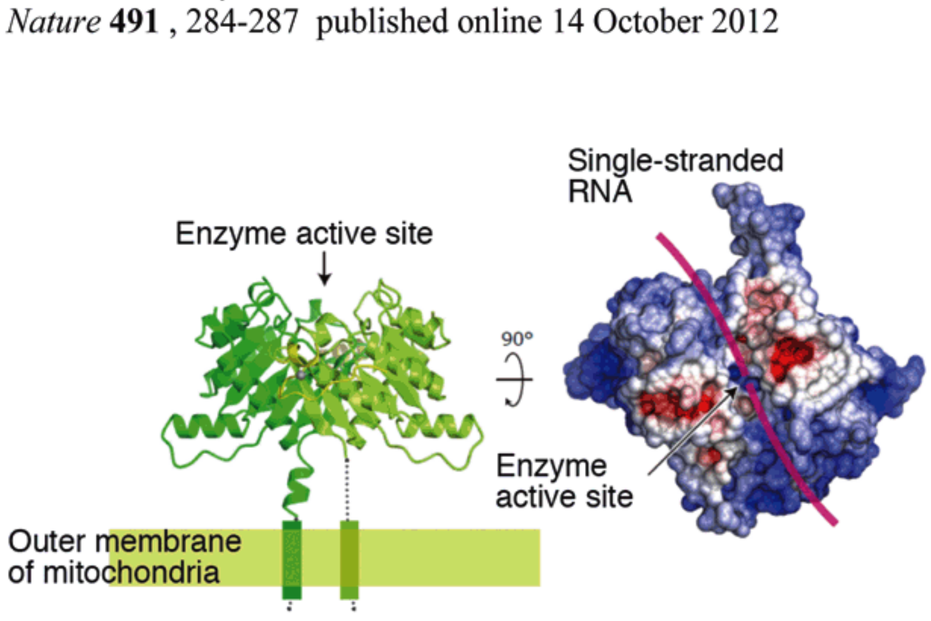


Fig.1 X-ray crystal structure of Zuc
(Left): a ribbon model.
(Right): a molecular surface model.

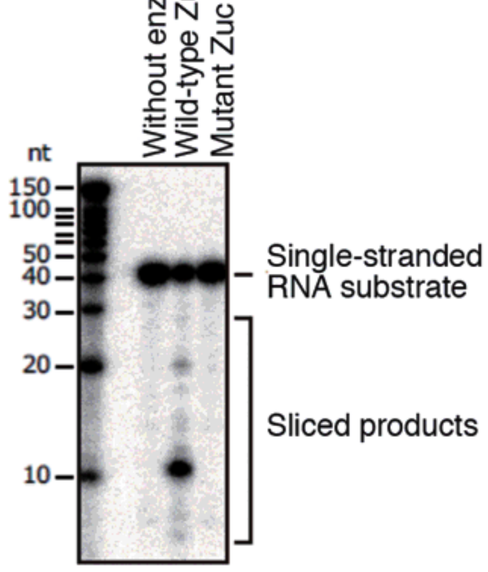


Fig. 2 RNA slicing activity of Zuc

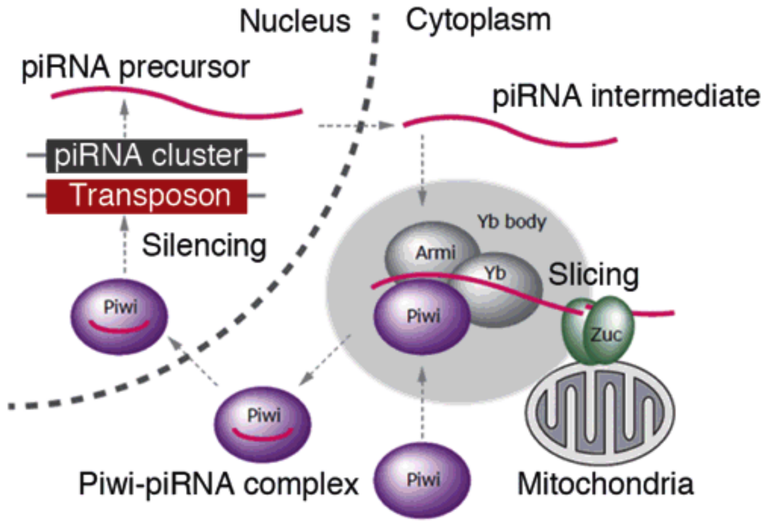


Fig. 3 piRNA production model