Structural insights into the mechanism of dsRNA processing by prokaryotic and eukaryotic RNase III enzymes

Xinhua Ji, Ph.D.

Center for Structural Biology, National Cancer Institute, National Institutes of Health, USA

Abstract: RNase III represents a family of double-stranded RNA (dsRNA)-specific endoribonucleases, exemplified by prokaryotic RNase III and eukaryotic Rnt1p, Drosha, and Dicer. They play important roles in RNA processing and maturation, post-transcriptional gene silencing, and defense against viral infection. For mechanistic studies, bacterial RNase III and yeast Rnt1p are valuable model systems for the entire family. Our structures show that substrate selection by RNase III and Rnt1p is independent of cleavage, allowing the recognition of substrates with different structures while preserving the basic mechanism of two-Mg^{2+}-ion catalysis. In general, four conserved amino acid side chains are required for the cleavage of each phosphodiester bond, and our structures reveal that these four side chains play identical roles in both RNase III and Rnt1p. In addition, our structures show how a third Mg^{2+} ion is involved in RNase III catalysis and how two more amino acid side chains are involved in Rnt1p catalysis. Furthermore, our structures determined at a stage immediately after dsRNA cleavage reveal atomic details of cleavage site assemblies, providing insights into the reaction trajectories of two-Mg^{2+}-ion catalysis, and our structures determined at various catalytic stages outline hypothetical pathways of dsRNA processing.

Biography: Dr. Ji earned his Ph.D. degree at the University of Oklahoma (1985-1990) and performed his postdoctoral research at the University of Maryland (1991-1994), where he became a Research Assistant Professor before joining the National Cancer Institute (NCI), National Institutes of Health (NIH). At the NCI-Frederick, Dr. Ji established his laboratory in the ABL-Basic Research Program in 1995, moved to the Center for Cancer Research in 1999, and gained tenure as an NIH Senior Investigator in 2001. He is a member of the American Crystallographic Association (since 1986), the Editor of NIH X-ray Diffraction Newsletter (since 2001), and a member of NCI RNA Biology Initiative Steering Committee (since 2018).

Research: Dr. Ji's research is focused on the structural biology of RNA biogenesis, with an emphasis on RNA-processing proteins and RNA polymerase-associated transcription factors, and structure-based development of therapeutic agents. His goal of structural analysis is to map the reaction trajectory or functional cycle of selected biological macromolecules, and that of drug discovery is to design, synthesize, and characterize novel anticancer and antimicrobial agents. So far, his laboratory has described the reaction trajectory and/or functional cycle of HPPK (an essential enzyme in the folate pathway of microorganisms but absent in mammals), Era (an essential GTPase that couples cell growth with cell division), RapA (a Swi2/Snf2 protein that recycles RNA polymerase during transcription), and bacterial and yeast RNase III enzymes. They have also designed prodrugs that kill cancer cells from within by releasing nitric oxide and made significant progress toward novel antibiotics targeting HPPK.