CARM1 Regulates mRNA Nuclear Retention in Paraspeckles

The mammalian nucleus is highly organized into chromosome territories and a number of distinct membrane-less nuclear bodies or sub-nuclear structures that can affect nuclear neighborhoods and gene regulation. Distinct nuclear bodies contain specific protein and RNA components that define particular nuclear processes. Paraspeckles, first identified in 2002, are composed of the long noncoding RNA (lncRNA) NEAT1 which confers structural integrity and multiple proteins, including PSP1α, p54nrb and PSF for its potential functions.

In many cells, mRNAs containing inverted Alu repeats (IRAlus) in their 3′-untranslated regions (3′-UTRs) are inefficiently exported to the cytoplasm. Such nuclear retention correlates with paraspeckle-associated protein complexes containing p54nrb. However, nuclear retention of mRNAs containing IRAlus is variable and how regulation of retention and export is achieved is poorly understood.

Lately a group led by Prof. CHEN Lingling at the Shanghai Institute of Biochemistry and Cell Biology (SIBCB), Shanghai Institutes for Biological Sciences, CAS reported one mechanism of such regulation via the arginine methyltransferase CARM1. They demonstrated that disruption of CARM1 enhances the nuclear retention of mRNAs containing IRAlus. CARM1 regulates this nuclear retention pathway at two levels: CARM1 methylates the coiled-coil domain of p54nrb, resulting in reduced binding of p54nrb to mRNAs containing IRAlus; CARM1 also acts as a transcription regulator to suppress NEAT1 transcription, leading to reduced paraspeckle formation. These actions of CARM1 work together synergistically to regulate the export of transcripts containing IRAlus from paraspeckles under certain cellular stresses, such as poly(I:C) treatment. This work demonstrates how a post-translational modification of an RNA binding protein affects protein-RNA interaction and also uncovers a mechanism of transcriptional regulation of the long noncoding RNA NEAT1.

Under the title “Protein arginine methyltransferase CARM1 attenuates the paraspeckle-mediated nuclear retention of mRNAs containing IRAlus”, this work was published in Genes & Development on March 15th 2015 and further highlighted in the April 1st issue of the same journal by a commentary (Elbarbary & Maquat. Genes Dev. 2015, 29:687–689). This study was supported by the grants from the Chinese Academy of Sciences (the Strategic Priority Research Program), the Ministry of Science and Technology, and National Natural Science Foundation of China.

A model of how the nuclear retention of IRAlus mRNAs at paraspeckles is regulated. Left, under normal conditions, CARM1 suppresses NEAT1 transcription and paraspeckle formation and also methylates p54nrb, resulting in the reduced binding capability to mRNAs containing IRAlus. Right, upon appropriate stimulation, such as upon poly(I:C) treatment, actions of CARM1 are attenuated, resulting in an increased expression of NEAT1 RNA, unmethylated p54nrb and enhanced nuclear retention of IRAlus mRNAs at paraspeckles.

(Image by courtesy of Prof. CHEN Lingling)