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Modulation of micro RNA/RNAi pathway

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RNA interference (RNAi) is a well-conserved mechanism that uses small noncoding RNAs to silence gene expression post-transcriptionally. Gene regulation by RNAi has been recognized as one of the major regulatory mechanisms in eukaryotic cells. Although the major components in RNAi/miRNA pathway have been identified, little is known about the regulation of the RNAi pathway itself. To dissect cellular components modulating RNAi using chemical biology approach, we have previously developed a cell-based assay to monitor the activity of the RNAi pathway. Several potent RNAi enhancers have been identified during the pilot screening from the 8,000 diversified compounds. Among them is a small-molecule enoxacin that enhances siRNA-mediated mRNA degradation and promotes the biogenesis of endogenous miRNAs. We show that this RNAi-enhancing activity depends on the trans-activation-responsive region RNA-binding protein. Our results provide a proof-of-principle demonstration that small molecules can be used to modulate the activity of the RNAi pathway and RNAi enhancers may be useful in the development of research tools and therapeutics. In addition to enoxacin, several other structurally distinct small molecules with metal/Fe chelating activity were found to significantly enhance RNAi activity as well in iron-dependent manner. Iron is essential for fundamental metabolic processes, and its homeostasis is tightly regulated. We show that cytosolic iron regulates the activity of the miRNA pathway through poly(C)-binding protein 2 (PCBP2). PCBP2 is associated with Dicer and promotes the processing of miRNA precursors. Cytosolic iron could modulate the association between PCBP2 and Dicer, as well as the dimerization of PCBP2 and its ability to bind to miRNA precursors, which can alter the processing of miRNA precursors. Our findings not only reveal an unexpected role for iron homeostasis in the regulation of miRNA biogenesis, but also suggest potential use of iron chelators to modulate the activity of the miRNA pathway.

Biography

Yujing Li, male, molecular biologist, completed his Ph.D from Institute of Genetics, Chinese Academy of Sciences, and got his Postdoc trainings at the University of Georgia and Emory University School of Medicine. Since January 2011, he has been serving as an editorial board member of Human Genetics and Embryology: Current Research. He has been invited /selected for speakers in several international conferences such as ASPB and ICHG/ASPB. He has published more than 30 of papers in peer-reviewed journals and some book chapters.

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