CDB SEMINAR


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16:00-17:30 Seminar Room A7F

## Rocaglates convert DEAD-box protein eIF4A into a sequence-selective translational repressor


**Summary**

Since Nobel Prize scientist Francis Crick has proposed, the central dogma of molecular biology has been the most common principle of life. Although, in the central dogma, it has been widely accepted that the protein expression level is simply determined by the abundance of mRNA, recent genome-wide and comprehensive analysis showed that mRNA abundance could only explain 30-40% of protein abundance. Moreover, the presence of frame-shift, stop codon read-through, and multiple translation initiation sites in mRNAs challenge the prediction of protein products from mRNAs. In addition to the impact of translation control to the final proteome in cells, the significance of translation regulation is evident from the fact that some translation drugs are also known as promising anti-tumor drugs. However, the gene regulation at the translation level is still poorly understood. Thus, the quantitative, genome-wide, and unbiased techniques to measure translation in cells are warranted. Indeed, recent development of a technique called ribosome profiling based on next-generation deep sequencer enables us to survey translation and its regulation in vivo.

Rocaglamide A (RocA) typifies a class of protein synthesis inhibitors that selectively kill aneuploid tumor cells and repress translation of specific mRNAs. RocA targets eukaryotic translation initiation factor 4A (eIF4A), an ATP-dependent DEAD-box RNA helicase, and its mRNA selectivity is proposed to reflect highly structured 5'UTRs that require eIF4A-mediated unwinding strongly. Here, by ribosome profiling and other deep sequencing based techniques, we show that secondary structure in 5'UTRs is only a minor determinant for RocA selectivity and RocA does not repress translation by reducing eIF4A availability. Rather, in vitro and in cells, RocA specifically clamps eIF4A onto polypurine sequences in ATP-independent manner. This artificially clamped eIF4A blocks 43S scanning, leading to premature, upstream translation initiation and reducing gene expression on transcripts bearing the RocA-eIF4A target sequence. In elucidating the mechanism of selective translation repression by this lead anti-cancer compound, we provide the first example of a drug stabilizing sequence-selective RNA-protein interactions.



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