Journal club

RNA interference

A catalytic function for mammalian Argonautes

The early 2000s were exciting times, thanks to the relatively recent discovery of RNA interference (RNAi): the ability of double-stranded RNA to trigger gene silencing. By 2010, many components of the RNAi machinery — including Dicer and the argonaute proteins — had been identified and shown to be highly conserved across species. Argonaute proteins, in particular, were found to contain a catalytic centre that could cleave target RNAs that have perfect complementarity to a bound small RNA. In mammals, argonaute-2 (AGO2) retained this conserved domain, and exploitation of the RNAi pathway soon became a popular and effective experimental approach to silence genes. So much so, that it is still in use and is bound to the clinic.

But a key question remained unanswered. Although in many organisms RNA cleavage by argonaute serves as an innate immunity mechanism against viruses and transposons, or to regulate endogenous gene expression, these functions seem to be largely absent in mammals. In fact, mammalian argonaute proteins of the Ago clade — to which AGO2 belongs — have been co-opted to silence genes through the microRNA (miRNA) pathway. Recognition of target RNAs by vertebrate miRNAs requires only partial sequence complementarity, which is insufficient to trigger cleavage. It was therefore unclear what the endogenous roles (if any) of the nucleolytic activity of mammalian AGO2 were.

To address this question, the Hannon lab engineered mice with a catalytic inactive *Ago2* allele. Homozygous mutants for this mutation died soon after birth with an obvious anaemia, providing the first evidence that catalysis by AGO2 was essential to vertebrates. It turned out that miR-451, a miRNA required for erythrocyte maturation, folds into an unusual hairpin structure that cannot be processed by Dicer. Instead, its biogenesis depends on AGO2-mediated cleavage, explaining the strong anaemia of the mutant mice.

> **"… there are other physiological requirements for the catalytic activity of AGO2 in mammals. What those are remains a mystery…"**

Curiously, we now know that anaemia is not the cause of lethality, which indicates that there are other physiological requirements for the catalytic activity of AGO2 in mammals. What those are remains a mystery, 14 years after the publication of this groundbreaking paper.

Joana A. Vidigal
NCI, NIH, Bethesda, MD, USA.
e-mail: joana.vidigal@nih.gov

Original article: Cheloufi, S. et al. A dicer-independent miRNA biogenesis pathway that requires Ago catalysis. *Nature* **465**, 584–589 (2010)

Development

Localized translation in the embryo

The developmental events required to build the beautiful and diverse body plans of adult animals depend on the first division events during embryogenesis. Remarkably, we know little about how these crucial establishment events are accomplished in mammalian embryos.

Seminal discoveries in *Drosophila melanogaster* and *Caenorhabditis elegans* showed that the establishment of the anteroposterior body axis requires precise morphogen gradients and asymmetric cell division, mediated by partitioning (Par) proteins. Morphogen gradients are established through the polarized localization of RNAs that are translated along the anteroposterior axis in early embryos. These RNA gradients are dependent on the position and concentration of the microtubule cytoskeleton. How microtubules, RNA localization and translation are coordinated and polarized in mammalian embryos remain unknown.

To uncover the mysteries behind the establishment of cell fate in mammalian embryos, Zenker and colleagues used high-resolution live imaging and 3D reconstruction of mouse embryos to demonstrate that RNA asymmetries are established in the 16-cell stage in the outermost blastomeres and require microtubule plus ends for transport. In addition, lysosomes, which are involved in the trafficking of membraneless RNA granules, were found to be necessary for basally directed RNA movement. Lastly, annexin A11, a previously described RNA granule tether, was found to be required for the establishment of RNA and lysosome distribution asymmetries in late 16-cell stage embryos. Loss of annexin A11 prevented the apicobasal asymmetries, and embryos failed to develop properly.

Next, the authors asked if different RNA varieties were found in basal and apical clusters in early mammalian embryos. In apical regions, mRNA and tRNA puncta were found, whereas basal regions were devoid of both types of RNA. rRNA was enriched in both apical and basal regions but a higher abundance of assembled ribosomal subunits was detected apically, and these apical regions were also found to be more translationally active.

The compartmentalization of RNA translation mechanisms and rRNA synthesis may be a determining factor of pluripotency, infertility and reproductive health in humans. These findings reveal the importance of localized RNA transport and translation in early mammalian development and broaden our understanding of the crucial and complex roles that localized translation has during asymmetric cell division.

Ahna Skop [1] & **Karen Schindler** [2]
[1]Laboratory of Genetics, University of Wisconsin-Madison, Madison, WI, USA. [2]Department of Genetics, Rutgers University, New Brunswick, NJ, USA.
e-mail: skop@wisc.edu; ks804@hginj.rutgers.edu

Original article: Hawdon, A. et al. Apicobasal RNA asymmetries regulate cell fate in the early mouse embryo. *Nat. Commun.* **14**, 2909 (2023)

Related article: Liao, Y.-C. et al. RNA granules hitchhike on lysosomes for long-distance transport, using annexin A11 as a molecular tether. *Cell* **179**, 147–164.e20 (2019)

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