Primary piRNA biogenesis: caught up in a Maelstrom

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Precursors for most Piwi-interacting RNAs (piRNAs) are indistinguishable from other RNA polymerase II-transcribed long non-coding RNAs. So, it is currently unclear how they are recognized as substrates by the piRNA processing machinery that resides in cytoplasmic granules called nuage. In this issue, Castaneda et al (2014) reveal a role for the nuage component and nucleo-cytoplasmic shuttling protein Maelstrom in mouse piRNA biogenesis.

See also: J Castaneda et al (September 2014)

Gamet cells are entrusted with the task of faithfully transmitting genetic information from one generation to the next. A major threat to germline genome integrity is the activity of mobile genetic elements called transposons, as they have the potential to cause mutations, usually leading to infertility. To counteract this threat, animal germlines have evolved a defense system composed of Piwi proteins and their associated piRNAs (Malone & Hannon, 2009). In their simplest form, piRNAs guide Piwi endonucleases to cleave transposon transcripts resulting in their degradation. More complex systems come into play when nuclear Piwi proteins mediate transcriptional silencing of target transposon loci by recruitment of H3K9me3 chromatin marks and/or DNA methylation.

How piRNAs are made is a problem that continues to intrigue researchers. We know that 50–100 kilobases, long-defined non-coding transcription units called piRNA clusters, are sources of most piRNAs. These are transcribed by RNA polymerase II, after which the capped and polyadenylated precursor transcripts are believed to be exported to cytoplasmic granules called nuage (‘cloud’ in French) where piRNA biogenesis factors reside (Li et al, 2013). The precursor is then converted into tens of thousands of mature primary piRNAs via a poorly understood primary biogenesis pathway. Importantly, how the nuclear history of transcription from a cluster locus is linked to the cytoplasmic fate of piRNA production is not known.

In this issue, Castaneda et al (2014) identify a role for the nuage component and nucleo-cytoplasmic shuttling protein Maelstrom (Findley et al, 2003) in mouse primary piRNA biogenesis.

Maelstrom (Mael) is a conserved factor essential for transposon silencing and fertility in both flies and mice, but its exact biochemical function remains a mystery (Lim & Kai, 2007; Soper et al, 2008). To examine this, Castaneda et al isolated Mael complexes from adult mouse testes and identified associated proteins by mass spectrometry. Miwi and tudor domain-containing protein 6 (Tdrd6) were dominant partners of this complex. This association is likely to be direct as it can be reproduced in transfected somatic human cells and is resistant to RNase treatment. By carrying out RNA sequencing after immunoprecipitation (RIP-seq), the authors revealed an enrichment of pachytene piRNA precursors (~100 nt long reads) in the Mael complexes. Interestingly, mature piRNA sequences are depleted in the RIP-seq libraries, indicating that precursors present in the Mael complexes are undergoing fragmentation/processing into primary piRNAs. Indeed, mice lacking mael display a drastic reduction (10-fold) in piRNA levels, with pachytene piRNAs being specifically affected. Based on these studies, a model for mouse primary piRNA biogenesis can be proposed where the nucleo-cytoplasmic shuttling protein Mael binds pachytene piRNA precursors and delivers them to the nuage for processing.

What is the consequence of loss of pachytene piRNAs? Mutant mice display malespecific infertility, and the arrested round spermatids show acrosome and flagellum formation defects. Ribosome profiling analysis in the mael mutant testes identified 880 mRNAs with reduced translation, many of which encode proteins needed for acrosome and flagellum formation. The precise reason for this translational inhibition is currently not known, but a direct role for Mael or sequence-specific implication of pachytene piRNAs in promoting translation is not among the suggested possibilities. Thus, the mystery surrounding pachytene piRNAs is only deepening.

As with other interesting studies, this work also opens up new questions that await answers. How can Mael distinguish pachytene piRNA precursors from other transcripts? Is there a coupling between transcription from the piRNA cluster promoter and fate of the precursor in the cytoplasm? How do other established primary piRNA biogenesis factors access precursors in the

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Mael complex? In fly ovaries, Mael is shown to be largely dispensable for piRNA biogenesis, but is implicated as an effector of nuclear Piwi-mediated transcriptional silencing of transposons (Sienski et al., 2012). Specifically, it was placed downstream of piRNA precursors in mice) and deliver them to cytoplasmic nuage. The individual fate of these RNAs is different in the fly and mouse systems.

Figure 1. Models for Maelstrom function in the animal germline. (A) Maelstrom is involved in transcriptional silencing of transposons in fly ovaries. The protein acts downstream of Piwi-mediated deposition of H3K9me3 chromatin marks. (B) In mouse male germ cells, Maelstrom is required for primary piRNA biogenesis as it is shown to bind precursors of pachytene piRNAs (in this issue). (C) Since Maelstrom is a nucleo-cytoplasmic shuttling protein, it can bind RNA substrates (transposons in fly ovaries or piRNA precursors in mice) and deliver them to cytoplasmic nuage. The individual fate of these RNAs is different in the fly and mouse systems.

MAEL domain abrogates its in vivo role in the fly ovaries (Sienski et al., 2012). Future structural and biochemical studies will be required to shed more light on what activities these domains provide.

References


