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Deciphering piRNA biogenesis through cytoplasmic granules, mitochondria and exosomes

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ABSTRACT

RNA systems biology is marked by a myriad of cellular processes mediated by small and long non-coding RNAs. Small non-coding RNAs include siRNAs (small interfering RNAs), miRNAs (microRNAs), tRFs(tRNA derived fragments), and piRNAs (PIWI-interacting RNAs). piRNAs are vital for the maintenance of the germ-line integrity and repress the transposons either transcriptionally or post-transcriptionally. Studies based on model organisms have shown that defects in the piRNA pathway exhibit impaired gametogenesis and loss of fertility. piRNA biogenesis is marked by transcription of precursor molecules and their subsequent processing in the cytoplasm to generate mature piRNAs. Their biogenesis is unique and complex, which involves non-canonical transcription and self-amplification mechanisms such as the ping-pong cycle. piRNA biogenesis is different in somatic and germ cells and involves the role of cytoplasmic granules in addition to mitochondria. In this review, we discuss the biogenesis and maturation of piRNAs in various cytoplasmic granules such as Yb and nuage bodies. Also, we review the role of P bodies, stress granules, and P granules, and membrane-bound compartments such as mitochondria and exosomes in piRNA biogenesis.

1. Introduction

Non-coding RNAs are endogenous RNA molecules that are not translated but still have specific cellular and molecular functions. These are classified as small non-coding RNAs (<200 nt) and long non-coding RNAs (>200 nt). Small non-coding RNAs include miRNAs (microRNAs), tRFs (tRNA derived fragments), tsRNAs (tRNA halves), siRNAs (small interfering RNAs), Y RNAs and piRNAs (PIWI-interacting RNAs) [1]. miRNAs and siRNAs are well established in RNAi silencing, and their association with RISC complex is well studied. The majority of miRNAs silence genes; on the contrary, the piRNAs silence transposon elements. Also, these bind to several RNA binding proteins and are seen in several cytoplasmic/nuclear granular components. Processing bodies and stress granules are cytoplasmic compartments that are critical for miRNA silencing. piRNAs use cytoplasmic granules such as nuage and Yb bodies for their synthesis. In the current review, we discuss the overall biogenesis of piRNAs and how the nuage and Yb bodies are used for the same. We also discuss the role of P bodies, stress granules, mitochondria, and exosomes in piRNA biogenesis. Throughout the review, we depict the essential RNA binding protein players.

2. piRNAs

The piRNAs (PIWI-interacting RNAs) are 23–36 nt long single-stranded, small non-coding RNAs with 2′-O-methylation at their 3′ends [2]. In contrast to other non-coding RNAs, which are processed from the double-stranded RNAs, dicer-dependent and bound by Argonaute proteins, piRNAs are transcribed from ssRNA transcripts, dicer-independent, and are bound to PIWI (P-element Induced WImpy testis in *Drosophila*) proteins. Unlike miRNAs and siRNAs, they have no secondary hairpin structures [3]. piRNAs are classified based on their origin and function as repeat-associated piRNAs, piRNAs derived from 3′ untranslated of mRNAs, piRNAs originated from intergenic long non-coding RNAs (pachytene piRNAs), and 21U RNA piRNAs. 21U RNA piRNAs are specific to the *Caenorhabditis elegans* [4]. discovered piRNAs in the testis of *Drosophila*. They showed the presence of small RNAs generated from Su (Ste) locus and these were silencing *Stellate* genes that are known to be involved in spermiogenesis. In 2006, four independent groups using RNA sequencing identified the piRNAs in the mouse and rat germ cells [5–9]. Subsequently, they were discovered in flies, mammals and found to be associated with PIWI clad Argonaute proteins, and the

Abbreviations: piRNAs, PIWI-interacting RNAs; PIWI, P-element induced WImpy testis in *Drosophila*; RISC, RNA induced silencing complex; Zuc, zucchini.

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