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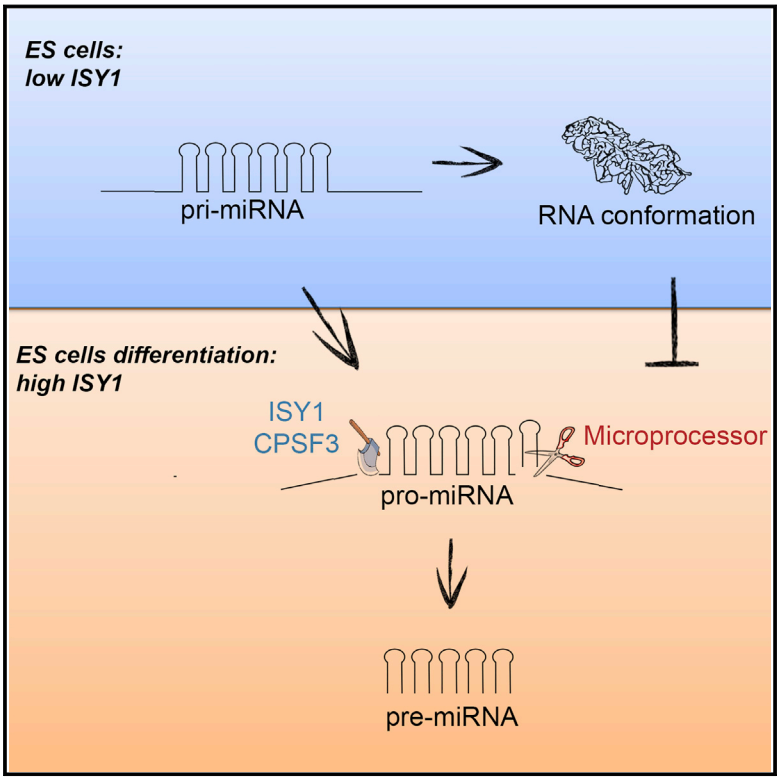
Cell

A Biogenesis Step Upstream of Microprocessor Controls miR-17∼92 Expression

Graphical Abstract



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In Brief

cis-acting sequences within a cluster-derived pri-miRNA can dynamically regulate expression of the constituent miRNAs and allow the uncoupled production of individual miRNAs from within the cluster during development.

Highlights

- Pri-miR-17∼92 adopts an RNA conformation that selectively blocks Microprocessor
- Pri-miR-17∼92 is processed to a progenitor-miRNA (pro-miRNA) intermediate
- The endonuclease CPSF3 and ISY1 are responsible for pro-miRNA biogenesis
- Pro-miRNA biogenesis controls miR-17∼92 expression during ESC differentiation

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A Biogenesis Step Upstream of Microprocessor Controls miR-17∼92 Expression

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SUMMARY

The precise control of miR-17∼92 microRNA (miRNA) is essential for normal development, and overexpression of certain miRNAs from this cluster is oncogenic. Here, we find that the relative expression of the six miRNAs processed from the primary (pri-miR-17∼92) transcript is dynamically regulated during embryonic stem cell (ESC) differentiation. Pri-miR-17∼92 is processed to a biogenesis intermediate, termed "progenitor-miRNA" (pro-miRNA). Pro-miRNA is an efficient substrate for Microprocessor and is required to selectively license production of pre-miR-17, pre-miR-18a, pre-miR-19a, pre-miR-20a, and pre-miR-19b from this cluster. Two complementary *cis*-regulatory repression domains within pri-miR-17∼92 are required for the blockade of miRNA processing through the formation of an autoinhibitory RNA conformation. The endonuclease CPSF3 (CPSF73) and the spliceosome-associated ISY1 are responsible for pro-miRNA biogenesis and expression of all miRNAs within the cluster except miR-92. Thus, developmentally regulated pro-miRNA processing is a key step controlling miRNA expression and explains the posttranscriptional control of miR-17∼92 expression in development.

INTRODUCTION

MicroRNAs (miRNAs) are a large family of regulatory RNAs that inhibit target expression by base pairing with complementary sites in the 3′ untranslated region (3′ UTR) to promote mRNA decay and translational repression (Bartel, 2009). Canonical miRNA biogenesis involves the two-step processing of long primary miRNA transcripts (pri-miRNAs) by the Microprocessor, comprising the ribonuclease DROSHA and its essential co-factor DGCR8, to generate 50–70 nucleotide (nt) precursor miRNA (pre-miRNA) intermediates that are processed by DICER to mature ∼22 nucleotide miRNAs (Ha and Kim, 2014). Individual pri-miRNA can be expressed from distinct miRNA loci, or from introns or exons of protein coding genes. Furthermore some pri-miRNAs contain a single miRNA whereas others contain clusters of several miRNAs. Regardless, Microprocessor recognizes the hairpin structures in the pri-miRNA through the stem-loop and the stem-loop-single-stranded RNA (ssRNA) junction and specifically cleaves the double stranded RNA stem to release the 5′ and 3′ flanking segments and generate pre-miRNAs that are substrates for DICER processing (Ha and Kim, 2014).

miRNAs play critical roles in development and their dysregulation causes disease (Di Leva and Croce, 2010; Lin and Gregory, 2015; Mendell and Olson, 2012). It is increasingly well appreciated that posttranscriptional mechanisms play an important role controlling miRNA expression (Siomi and Siomi, 2010). Several Microprocessor or Dicer accessory factors and inhibitory proteins have been identified that either facilitate or inhibit distinct subsets of miRNAs. The activity of some of these factors is linked with cell-signaling pathways to afford dynamic control of the miRNA biogenesis machinery (Mori et al., 2014; Siomi and Siomi, 2010). Perturbation of these pathways can be oncogenic. One example is the posttranscriptional control of let-7 miRNA expression by the RNA-binding protein LIN28 (Thornton and Gregory, 2012).

To investigate how expression of other miRNAs might be regulated, we focused on the polycistronic miR-17∼92. Pri-miR-17∼92 encodes six (miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, and miR-92a) mature miRNAs. Haploinsufficiency of this locus causes the Feingold syndrome of microcephaly, short stature, and digital abnormalities in human patients and mouse models, whereas ablation of this locus in mouse causes perinatal lethality with heart, lung, and B cell defects (Concepcion et al., 2012; de Pontual et al., 2011; Mendell, 2008; Ventura et al., 2008). Conditional mouse knockouts highlight the importance of these miRNAs for kidney development and function and neural stem cell biology (Bian et al., 2013; Marrone et al., 2014; Patel et al., 2013). Gene amplification and increased expression of miRNAs from this cluster is observed in numerous types of cancer compared to normal tissues, and transgenic overexpression of this "OncomiR-1" promotes B cell lymphoma, T cell acute lymphoblastic leukemia (T-ALL), and retinoblastoma in mice (Conkrite et al., 2011; He et al., 2005; Mavrakis et al., 2010; Nittner et al., 2012; Sandhu et al., 2013). Individual miRNAs within this cluster promote cell proliferation, inhibit apoptosis, inhibit differentiation, and promote angiogenesis, to drive tumorigenesis (Mendell, 2008; Mu et al., 2009; Olive et al., 2009).