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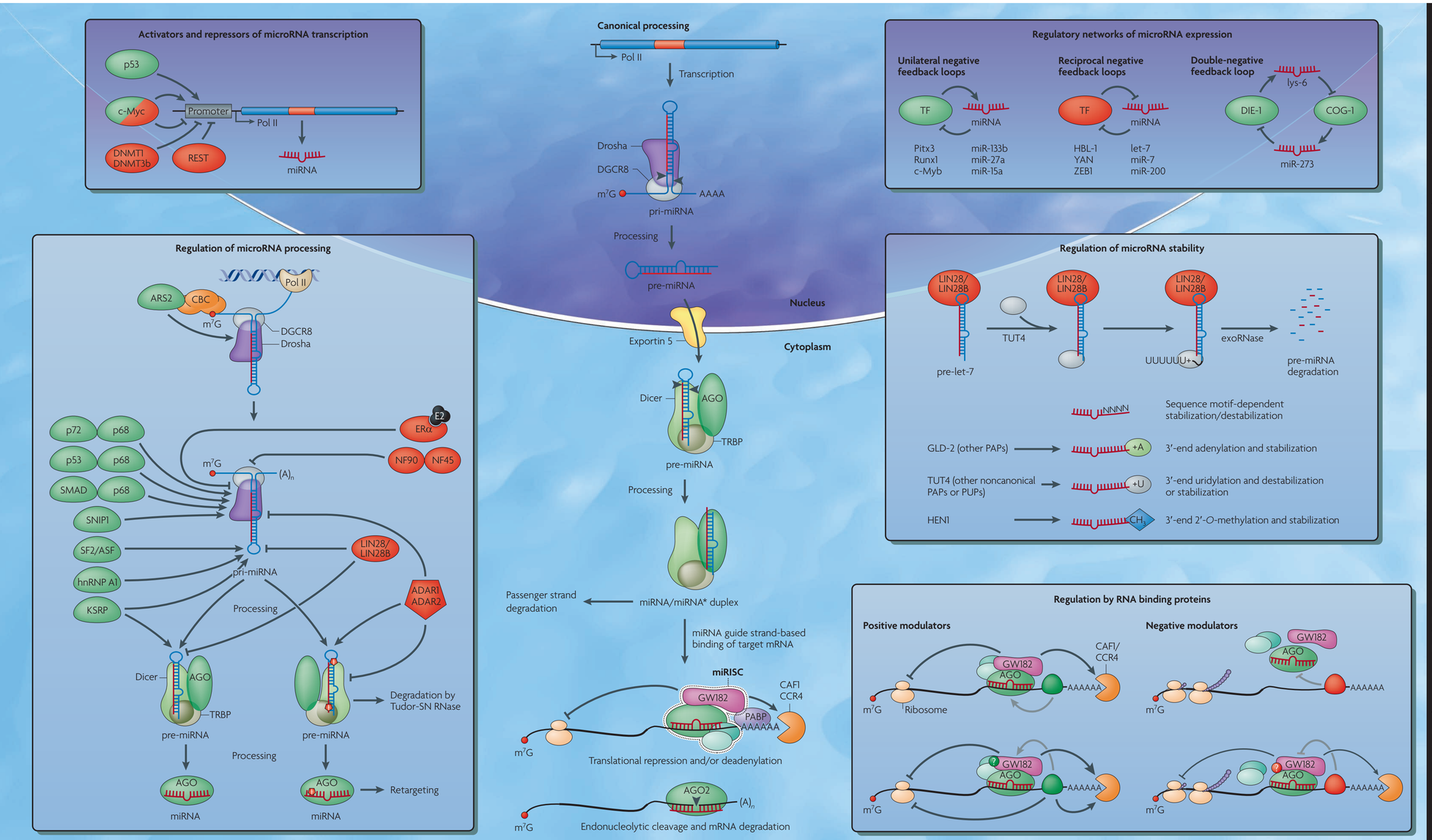
Regulation of microRNA biogenesis, function and degradation

Jacek Krol, Inga Loedige and Witold Filipowicz

MicroRNAs (miRNAs) are a large family of post-transcriptional regulators of gene expression that are ~21-nucleotides in length and control many developmental and cellular processes in eukaryotes. The implication of miRNAs in many disease processes also makes them important potential targets for therapy. Research during the last decade has identified many of the components that participate in miRNA biogenesis and has established basic principles of miRNA function[1]. More recently, it has become apparent that miRNA regulators themselves are subject to sophisticated control. Many studies over the last few years have reported the regulation of miRNA biogenesis, function and degradation by a range of mechanisms involving numerous protein-protein and protein-RNA interactions[2]. Such regulation has an important role in the context-specific functions of miRNAs and an understanding of this control is needed to gain a full picture of the roles of miRNAs in development, physiology and disease.



MicroRNA biogenesis and function

MicroRNAs are processed from precursor pri-miRNAs, which are either transcribed from independent miRNA genes or are portions of introns of protein-coding RNA polymerase II (pol II) transcripts. The pri-miRNAs are processed to mature miRNAs by the RNaseIII family enzymes, Drosha and Dicer. The pre-miRNA product of Drosha cleavage is exported to the cytoplasm, where Dicer processes it to a miRNA/miRNA* duplex of ~20 bp. One strand of this duplex, the mature miRNA, is then incorporated into the miRNA-induced silencing complex, miRISC. Within miRISC, miRNAs base-pair to target mRNAs and induce their translational repression or deadenylation and degradation. Argonaute (AGO) proteins and GW182 proteins are key factors in the assembly and function of miRISCs.

Activators and repressors of microRNA transcription

Transcription of miRNA genes is regulated similarly to that of protein-coding genes and is a major level of control responsible for tissue- or development-specific expression of miRNAs. Many transcription factors (TFs) and other proteins regulate miRNA expression positively (green) or negatively (red) in a tissue- or developmental-specific manner. For example, the TFs c-Myc, N-Myc, p53 and REST, and the DNA methyltransferases DNMT1 and DNMT3b.

Regulatory networks of microRNA expression

Autoregulatory feedback loops are particularly important during cell fate determination and development. miRNAs are uniquely suited to participate in feedback circuits as they can directly base-pair with and repress mRNAs that encode factors involved in the biogenesis or function of the same miRNAs. For instance, the Pitx3 TF and miR-133b form a negative autoregulatory loop that controls dopaminergic neuron differentiation. More sophisticated regulation is provided by double-negative feedback loops like the one involving miRNAs lys-6 and miR-273, and TFs DIE-1 and COG-1 in C. elegans, which is instrumental in determining cell fate decisions between two alternative types of chemosensory neurons.

Regulation of microRNA processing

Pri-miRNA processing is linked to the 5′-terminal capping of transcripts. Arsenite-resistance protein 2 (ARS2), a component of the nuclear cap-binding complex, interacts with Drosha and is required for pri-miRNA stability and processing in flies and mammals. Drosha and Dicer generally operate in complexes with double-stranded RNA binding proteins (dsRBPs), such as DGCR8 and TRBP. The levels and activities of all these proteins are subject to regulation that affects the accumulation of miRNAs. A number of accessory proteins also regulate miRNA processing, either positively (green) or negatively (red), by interacting with Drosha, Dicer or miRNA precursors. The best-studied negative regulator is Lin-28, which has important roles in regulating levels of the let-7 miRNA in stem cells and other progenitors. One of the positive regulators, the p68/p72 helicases, which frequently recruit several other regulatory proteins, are thought to stimulate the processing of one third of murine pri-miRNAs. Editing of pri- or pre-miRNAs by adenosine deaminases (ADAR1 and ADAR2) can affect the accumulation of mature miRNAs and possibly also miRNA target specificity.

Regulation of microRNA stability

The post-transcriptional addition of nucleotides to the 3′ ends of pre-miRNAs or mature miRNAs affects miRNA stability or abundance. Lin28 promotes uridylation of pre-let-7 in C. elegans and mammalian cells by recruiting the poly(U) polymerase (PUP) TUT4, which adds multiple U residues to the 3′ end of RNA substrates, preventing Dicer processing and inducing precursor degradation. RNA stability is also influenced by 3′-end sequence motifs or modifications that mark miRNAs for degradation or protect them against exonucleolytic activity, depending on the specific miRNAs and tissue.

Regulation of miRISC by RNA binding proteins

RBP binding to mRNAs can facilitate (green) or counteract (red) miRISC activity. RBPs that enhance repression by miRNAs (for example, FMRP and PUF) could facilitate or stabilize miRISC binding. Enhancement of silencing could also occur by strengthening interactions between miRISC components and downstream effectors. This might involve post-translational modifications of protein components (small green circle with question mark). Recruitment of translational repressors or deadenylation factors by RBPs independent of miRISC would also increase target repression. RBPs counteracting miRISC function can either prevent miRISC binding or might displace miRISC from mRNA, as exemplified by Dnd1 (dead end 1) and HuR (Hu antigen R) Other proteins could interfere with the interaction between miRISC components and downstream effectors. Alternatively, they might promote post-translational modification of miRISC components (small red circle with question mark).

Abbreviations

CBC, cap-binding complex; ERα, estrogen receptor α; hnRNP A1, heterogeneous nuclear ribonucleoprotein A1; m7G, 7-methylguanosine cap; PABP, poly(A) binding protein; SNIP1, SMAD nuclear interacting protein 1; TRBP, transactivation-responsive RNA-binding protein.

References

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