microRNA Functions

Philipp Möller

January 12, 2010

Contents

1 Introduction

1.1 What?

- non-coding, single-stranded RNA molecules
- 21-24 nucleotides
- regulate gene expression posttranscriptional

1.2 Biogenesis

RISC. *ribonucleinprotein complex required for small RNA-mediated gene silencing*

miRNA is generally transcribed as a primary transcript (pri-miRNA) through Pol II and processed to a 70-nucleotide stem-loop by the Microprocessor (Drosha/Pasha). The resulting pre-miRNA is transported into the cytoplasm via Exportin-5. Dicer proceeds to cleave the pre-miRNA to produce a mature miRNA:miRNA* duplex. TRBP/Loquacious is then used to bind the miRNA to Argonaute (Ago2) and RNA-induced silencing complex (RISC) is formed. The miRNA* strand is degraded.

1.3 Other Small Noncoding RNAs

- Small interfering RNA (siRNA)
- Piwi-interacting RNA (piRNA)

2 Target Identification

miRNA target. *a messenger RNA encoding a protein, containing target sites for and regulated by an miRNA*

miRNA seed. *seven to eight nucleotides at the 5' end of an miRNA that serve as the primary determinant of target specificity*

miRNA targets ar either indentified by

a 5' dominant sites, which base-pair precisely to the seed of the miRNA, with or without 3' pairing support or

b 3' compensatory sites, which have insufficient 5' pairing compensated for by strong pairing to the miRNAs' 3' region.

It is estimated that more than 30% of animal genes are miRNA targets.

3 Modes of Function

Different miRNAs will show different behaviour. The next sections discuss conceptually different modes of miRNA functions and outline various examples for each mode.

3.1 Developmental Switches

miRNAs required for developmental decision-making are expected to cause strong phenotypes. An example is *lin-4* in *C. elegans* which is required to downregulate *lin-14*. Without this downregulation a differentiation defect hinders the transition from the first to the second larval stage.
Other examples in *C. elegans* include:

- *let-7*: several genes affected and various symptoms depending on stage of development
- *lsy-6*: gustatory neurons ASEL and ASER

3.2 Fine Tuning

robustness. *invariance of phenotype in response to changing conditions or altered gene dosage*

Computational studies suggest that many miRNAs regulate a large sets of targets which are expressed at low levels in the miRNA-expressing cells. In these cases miRNA mutation would have subtle and hard to study phenotypes.

The *miR-430* multigene family is expressed in high levels in zebrafish embryos at the beginning of zygotic transcription. Several hundred targets are misregulated if *miR-430* is depleted.

3.3 Proliferation/Apoptosis

Hippo signaling pathway. *signal transduction mechanism that controls cell growth in animals*

In *Drosophila* overexpression of the miRNA *bantam* causes tissue overgrowth and the proapoptotic gene *hid* contains 5 five *bantam* target sites. *bantam* is also regulated by the Hippo signaling pathway. While the silencing of *hid* is not enough to cause cell grow it is suspected that *bantam* also regulates genes that cause positive growth.

3.4 Feedback Loops

Several miRNAs are part of regulatory feedback loops.

- *lsy-6* and *miR-273* in *C. elegans*: double negative-feedback loop, switch-like (See 3.1)

- *miR-7* in *Drosophila*: reciprocal negative-feedback loop, tuning-like (See 3.2), affects photoreceptor differentiation

3.5 Tresholding

miR-9a in *Drosophila* introduces a treshold that must be overcome by the expression of *senseless*. *miR-9a* is not part of the feedback loop itself but sets a limit for the activation of the transcriptional feedback system. This effect hasn't been shown to occur with other miRNAs yet.

4 miRNA in Human Diseases

4.1 Tourette's Syndrome

miRNAs have been implicated in Tourette's sydrome. The 3' UTR of SLITRK1 which contains an *miR-189* binding site is mutated and is stronger regulated. This mutation is only one out many factors that lead to this disease.

4.2 miRNAs as Oncogenes and Tumor Suppressors

Global miRNA expression levels are altered in primary human tumors and miRNA profiling may has diagnostic and prognostic potential. It is unknown if miRNA is actually involved in tumor formation.

4.3 miRNAs and Viruses

miRNA is used by viruses in their effort to control the host cell and vice versa by the host cell to defend against viruses.

miRNAs have only been found in nuclear DNA viruses (e.g. *herpes*), as RNA viruses are restricted to the cytoplasm and miRNAs require processing by Drosha in nucleus.

- *miR-S1* hides infected cells from the imune system
- *miR-32* restrict the replication of *PFC-1*

References

[1] Natascha Bushati, Stephen M. Cohen, *microRNA Functions*