

# microRNAs

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# What miRNAs are

- Small non-coding RNA found in most eucaryotic organisms
- ~22nt length

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- Biogenesis separate them from siRNA

# miRBase

- The miRBase database is a searchable database of published miRNA sequences and annotation.
- <http://www.mirbase.org/>
- They also have a naming service for new miRNAs

# What miRNAs do

- Bind to complementary sequences of target mRNAs
- Causes translational repression or target degradation and gene silencing

# miRNA expression

- Different sets of expressed miRNAs are found in different cell types and tissues
- Aberrant expression of miRNAs has been implicated in diseases

# Roles

- It is believed that miRNAs play critical roles in multiple biological processes
  - cell cycle control
  - cell growth and differentiation
  - apoptosis
  - embryo development
  - a number of other processes

# Related to disease

- There are indications that miRNAs may play crucial roles in human disease
  - Development
  - Progression
  - Prognosis
  - Diagnosis
  - Evaluation of treatment response
- miRNA-based therapies are under investigation

# Evolution

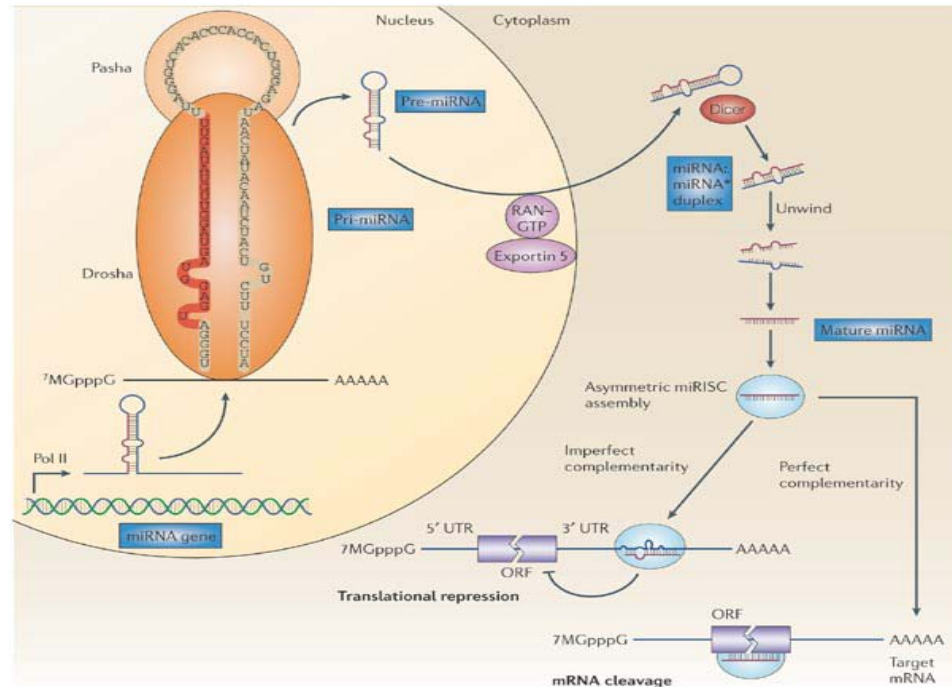
- miRNAs originate predominantly by random formation of hairpins in "non-coding" DNA, but also by the duplication and modification of existing miRNAs
- Due to low rate of evolution, many miRNAs are significant phylogenetic markers



# Rate of evolution

- New miRNA: Comparable to other ncRNA
- Old miRNAs: Lower rate of evolution
- When a miRNA gains function it is rarely lost from an animal genome

# miRNA in making



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# Biosynthesis

- Most common pathway
  - 1. primary-miRNA
    - An about 100nt long RNA sequence with a 5'cap and a poly A tail
  - 2. precursor-miRNA
    - An about 70nt long RNA sequence that forms a hairpin loop structure
  - 3. mature miRNA
    - An about 22nt long RNA sequence cut from either the 3p or the 5p side of the hairpin

# pri-miRNA

- miRNAs, transcribed by RNA polymerase II, are initially made as longer RNA transcripts called pri-miRNAs
- The pri-miRNA structure has a 5'cap and a poly-A tail
- miRNA embedded in hairpin structured motifs
- Can contain several miRNA precursors



# Pre-miRNA

- The pri-miRNAs are processed in the nucleus, by Drosha
- They are made into ~70nt long pre-miRNAs, which fold into imperfect hairpin loops
- The pre-miRNAs are then exported into the cytoplasm by the RAN GTP-dependent transporter exportin 5

# Mature mRNA

- The double-stranded RNA (miRNA/miRNA\* duplex) is excised from the pre-miRNA hairpin by another RNase III enzyme called Dicer

# The mature and the \*

- miRNA:miRNA\* duplex is incorporated into the miRISC complex.
- The mature miRNA strand is preferentially retained in the functional miRISC complex

# RISC

- RNA-induced silencing complex
- Dicer processing of the pre-miRNA is thought to be coupled with unwinding of the duplex, and generally one of the strands is incorporated into the RISC
- The other strand of the duplex (passenger strand) is normally degraded



# Movie

- <http://www.youtube.com/watch?v=-9pROnSD-A>

# mRNA targets, metazoan

- The miRNA seed region must match
- The seed is base 2 to base 7
- Usually matches in the 3'UTR
- Mostly inhibits protein translation

# mRNA targets, plants

- The whole miRNA matches
- Usually complementary to coding regions
- Mostly leads to cleavage

# Nomenclature

- The form of miRNA names is:
  - Three letter code for organism
  - mir (precursor) or miR (mature)
  - Number (sequential, mir-21 discovered before mir-92)
- hsa-mir-21
  - hsa is for **Homo Sapiens**
  - mir means we are talking about the precursor
  - 21 suggests this miRNA was discovered early

# Nomenclature

- Identical mirs from different species will be given the same number, for example hsa-mir-121 and xla-mir-121
- Identical mature sequences from distinct precursors will get names of the form hsa-miR-121-1 and hsa-miR-121-2
- Highly similar sequences will have the form hsa-miR-121a and hsa-miR-121b
- Plant miRNA names are of the form MIR121

# 3p and 5p

- The mature and the mature \* sequences are usually named with an additional -3p or -5p suffix to distinguish between them
- hsa-mir-21-3p
- hsa-mir-21-5p

# miRNA families

- miRNAs are grouped into families
- Original definition of family is sequences that have evolved from a common ancestor
- Some uses the seed sequence to group into families