

The role of RNA-binding miRNAs in early embryogenesis

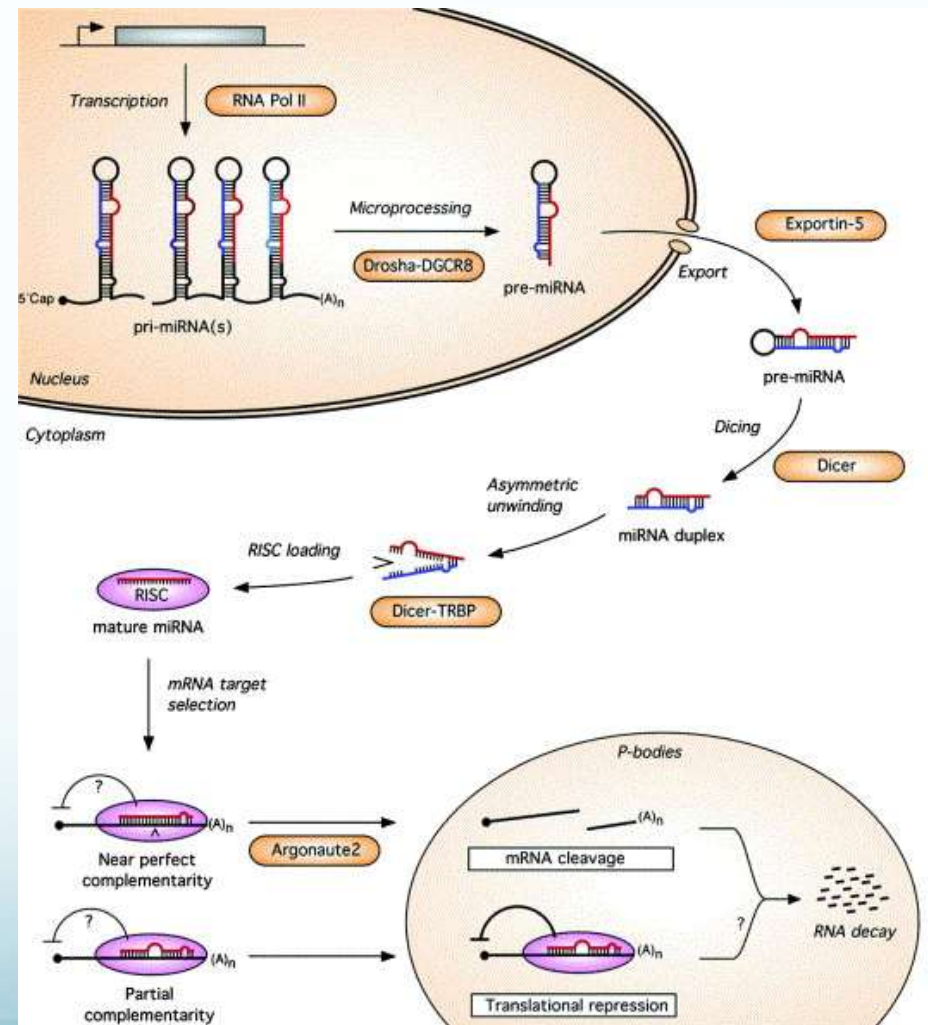
Embryo Physics lecture series, 04/16/14

Outline

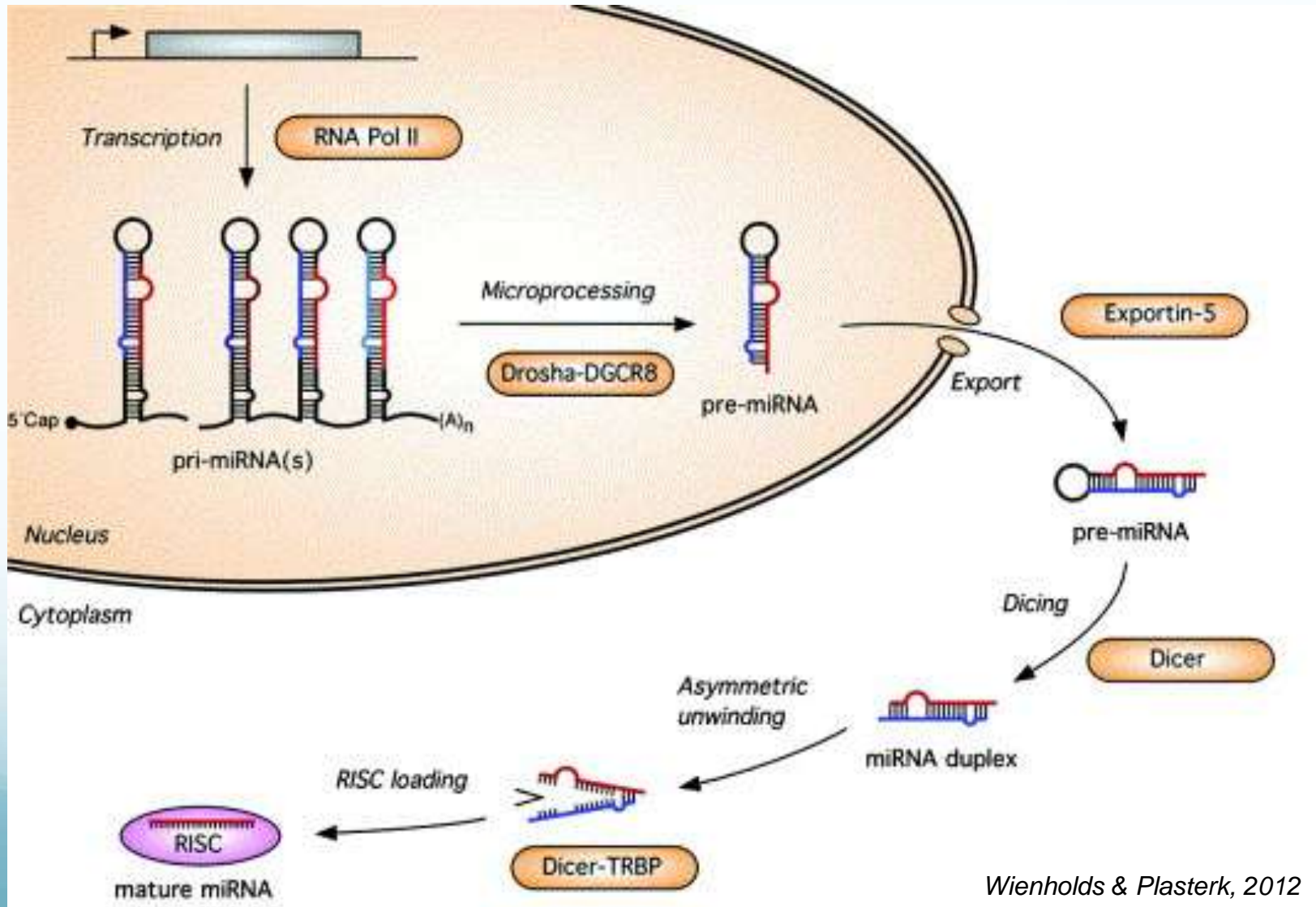
- miRNA
 - biology, biogenesis, and binding
- miRNA and embryogenesis
 - regulation of developmental genes
 - clearance of maternal RNA
- miRNA and disease

miRNA biology

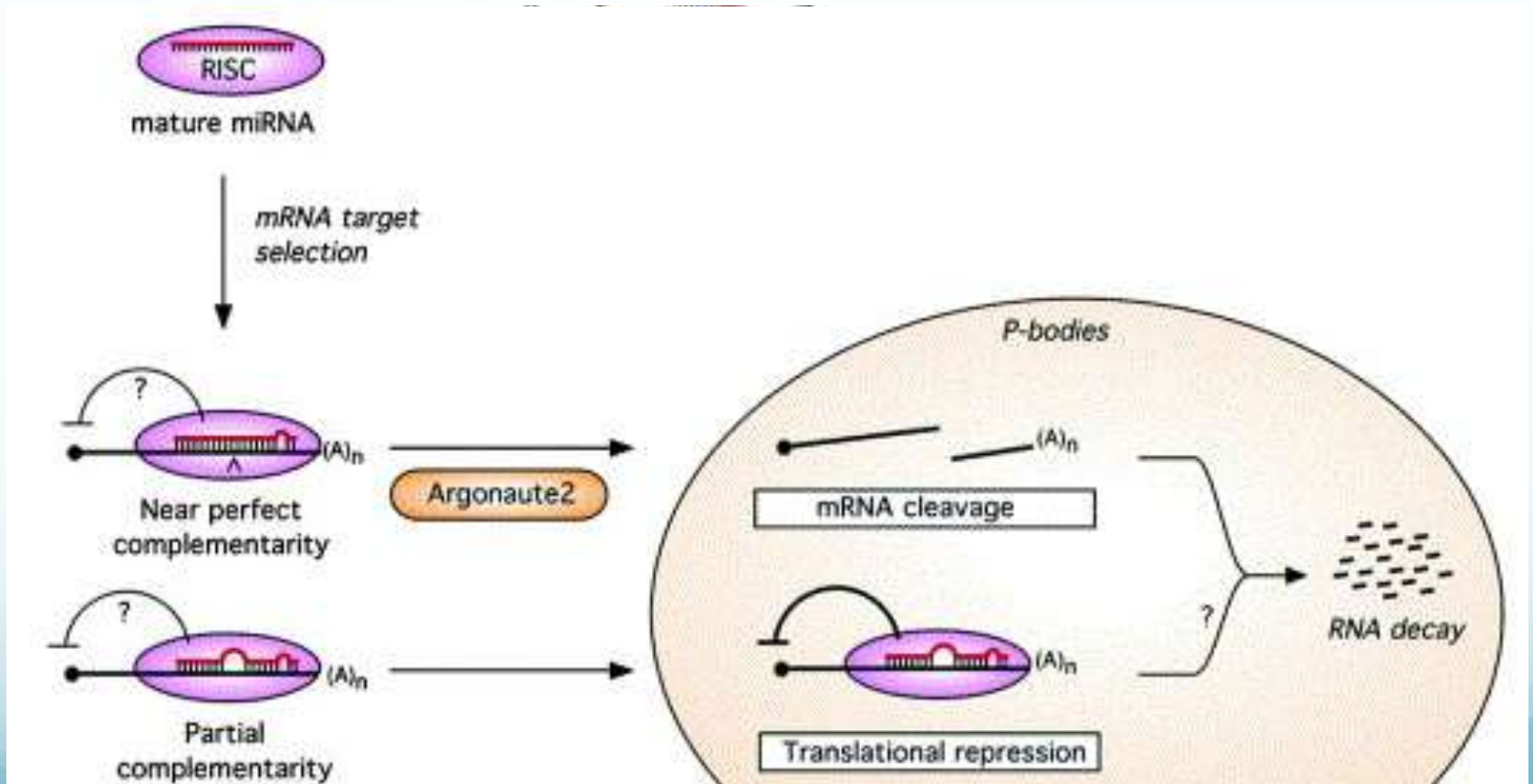
- miRNAs are short (usually 18-32 nucleotides) sequences with gene regulatory function
- ~1000 miRNAs have been identified in the humans
- Tend to be negative regulators, binding to mRNAs and targeting them for degradation
- Expression of certain miRNAs can be an indicator of expression for certain target genes



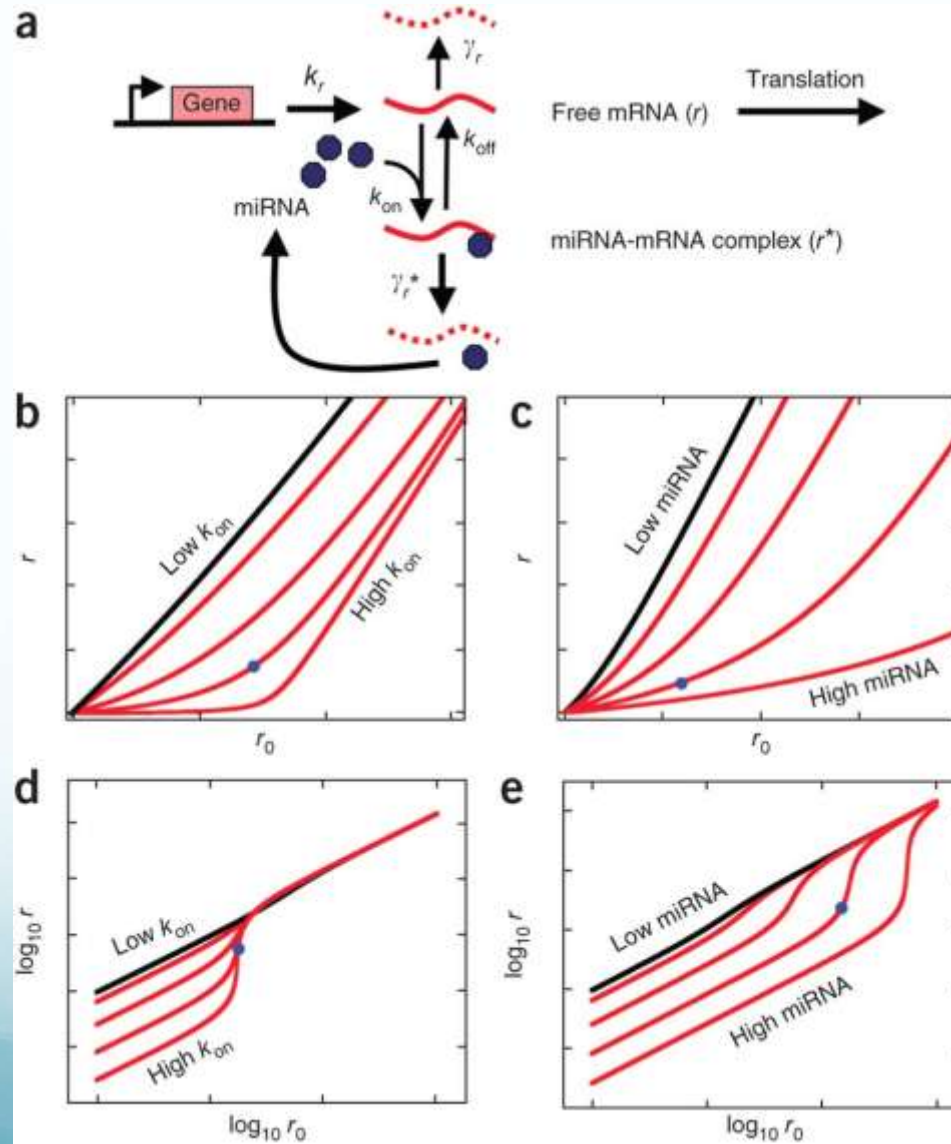
miRNA biogenesis



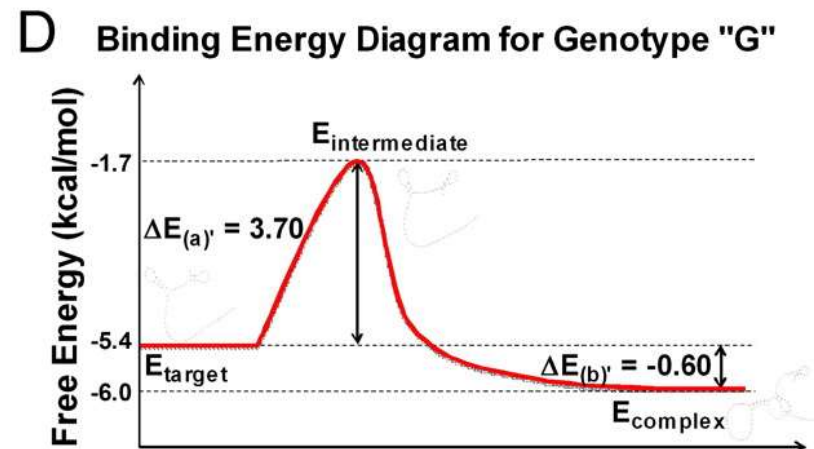
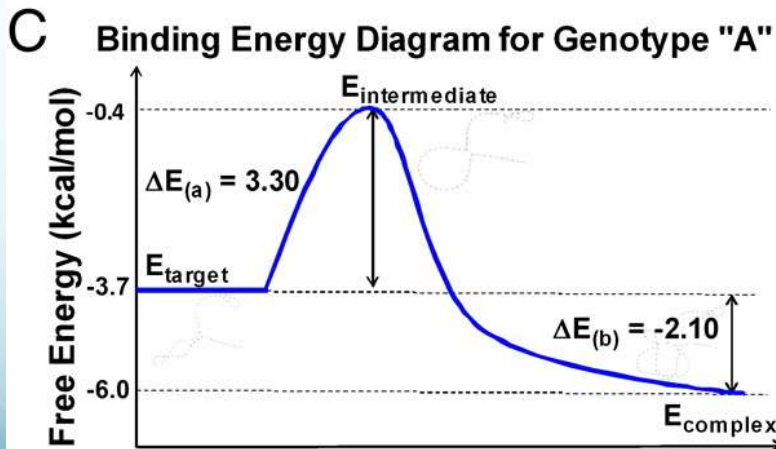
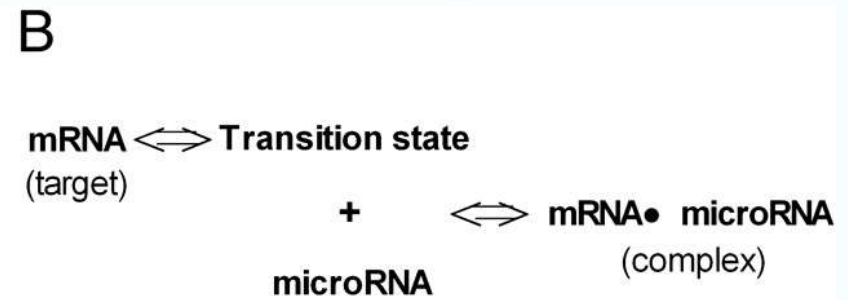
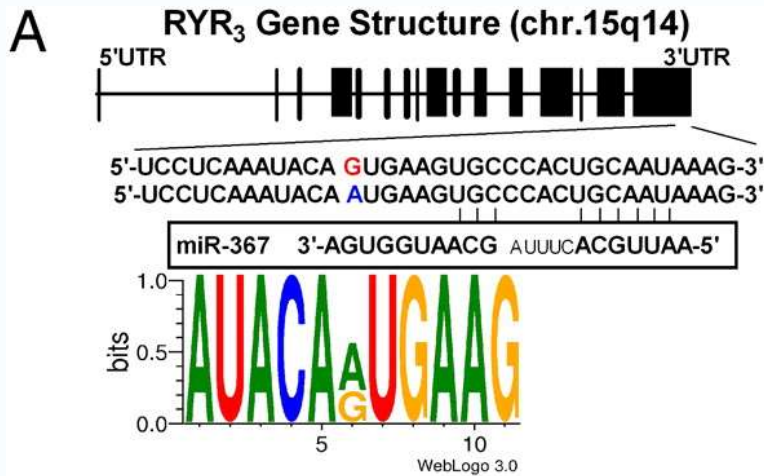
miRNA binding



Factors affecting miRNA binding

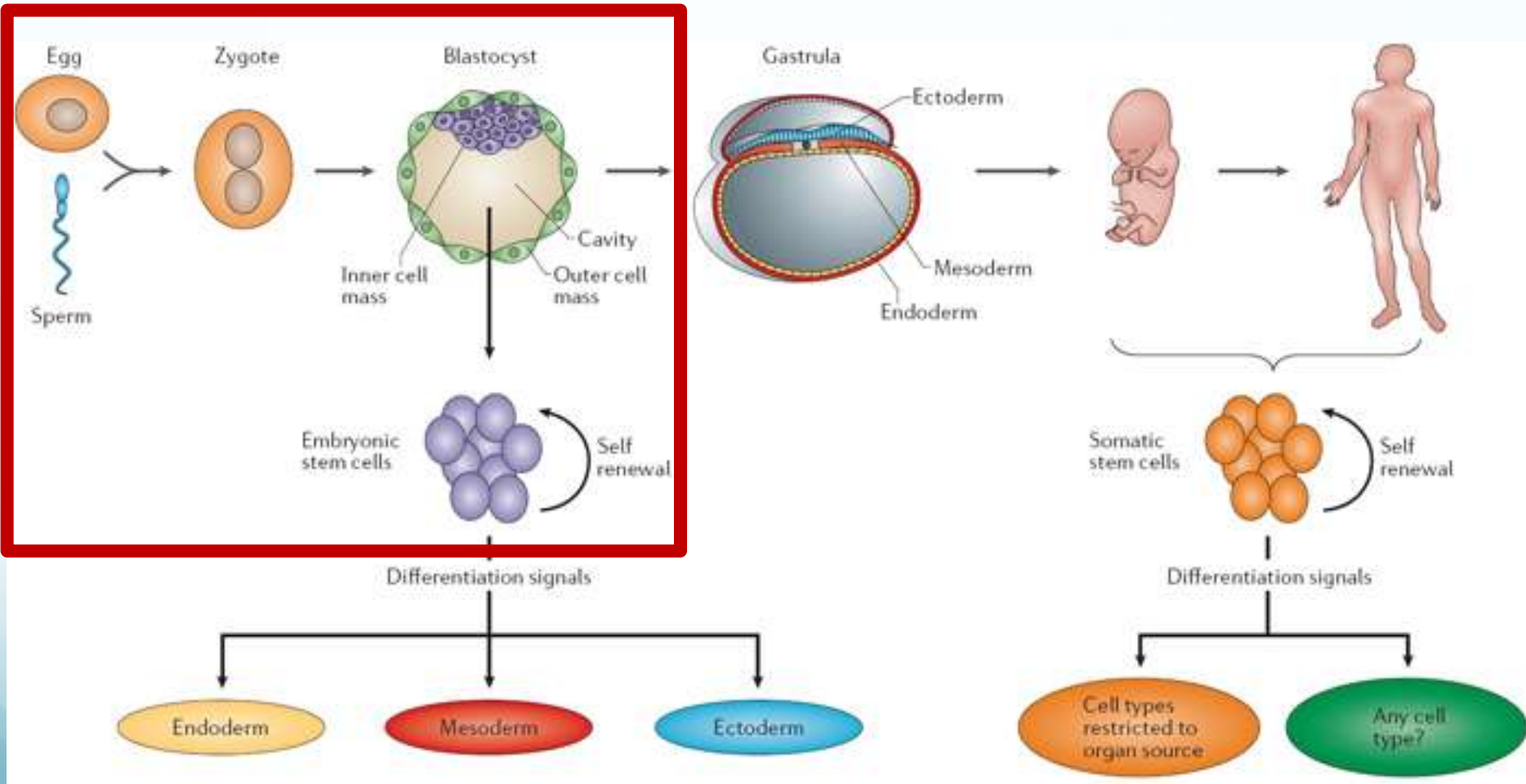


Allele-specific miRNA binding



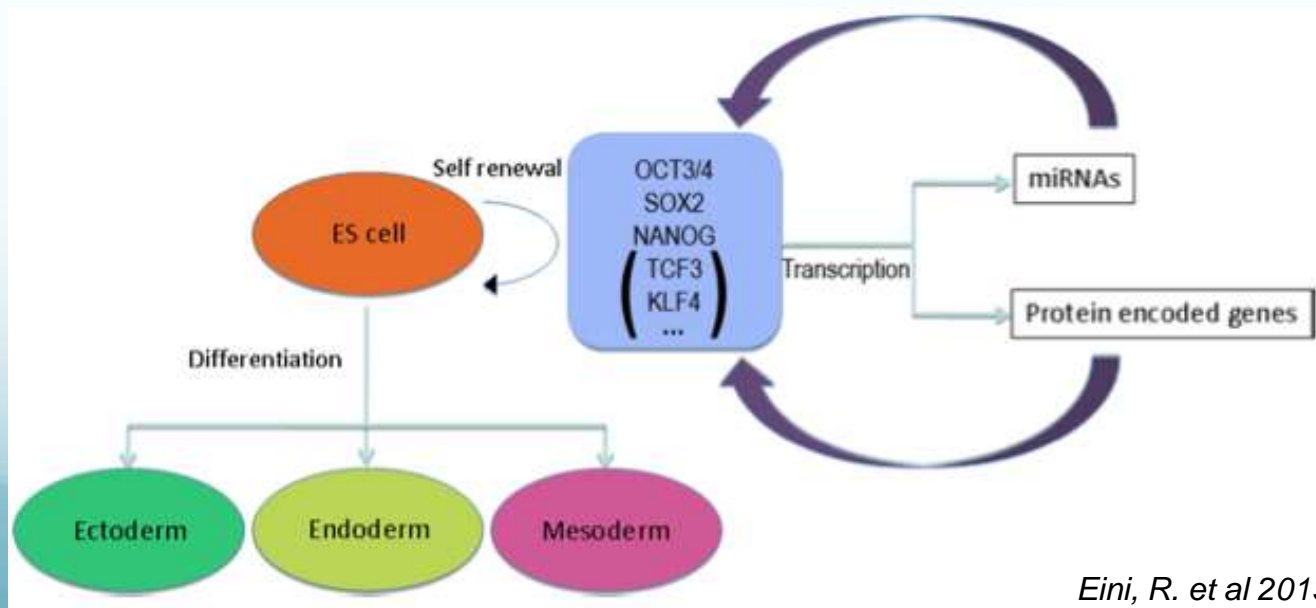
miRNA and early embryogenesis

Early embryogenesis

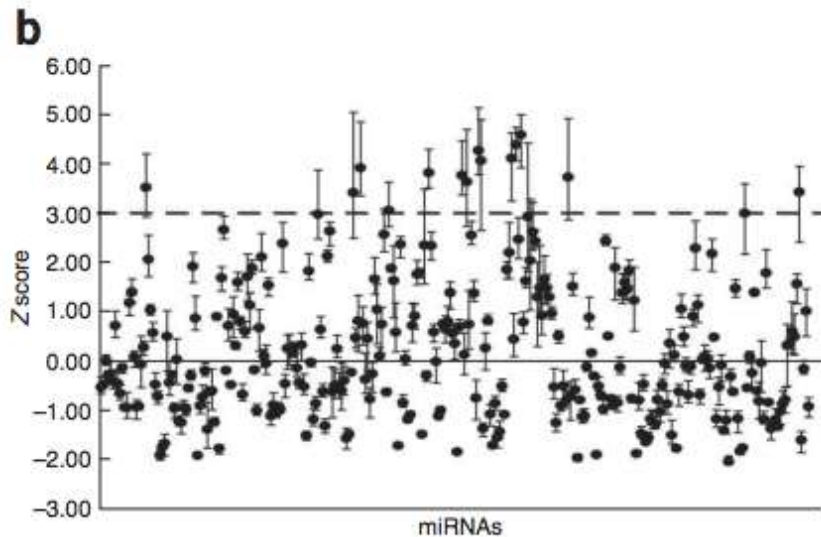


Role of miRNAs in development

- 31 miRNAs are reported to be specific to embryonic stem cells (ESCs)
 - miR-302 cluster and miR-371 cluster
- Importance of ESC-miRNAs established through Dicer and Dgcr8 knockouts in mice

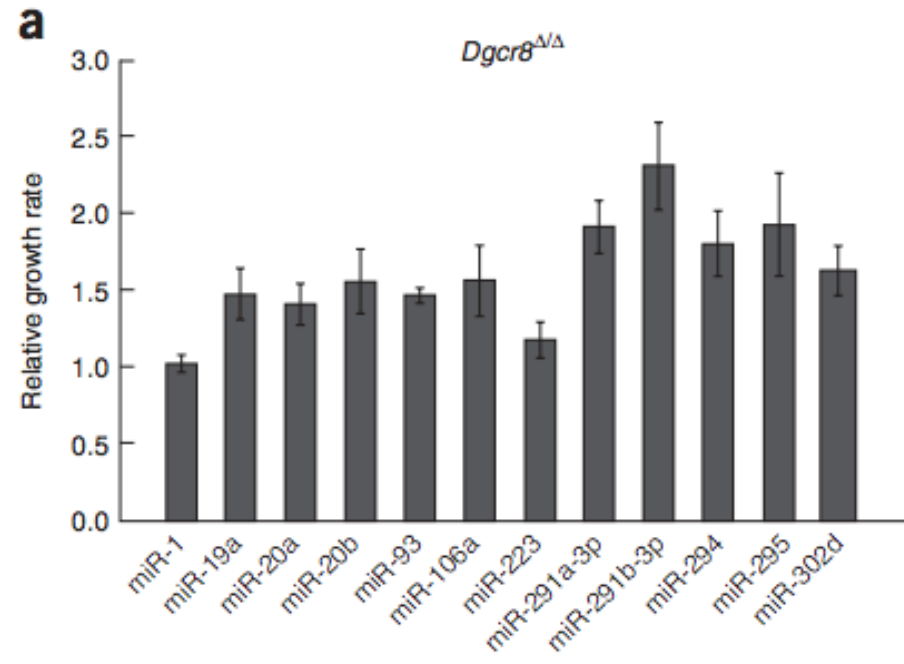


miRNA cluster miR-302 aids rapid proliferation of ESCs in developing embryo...



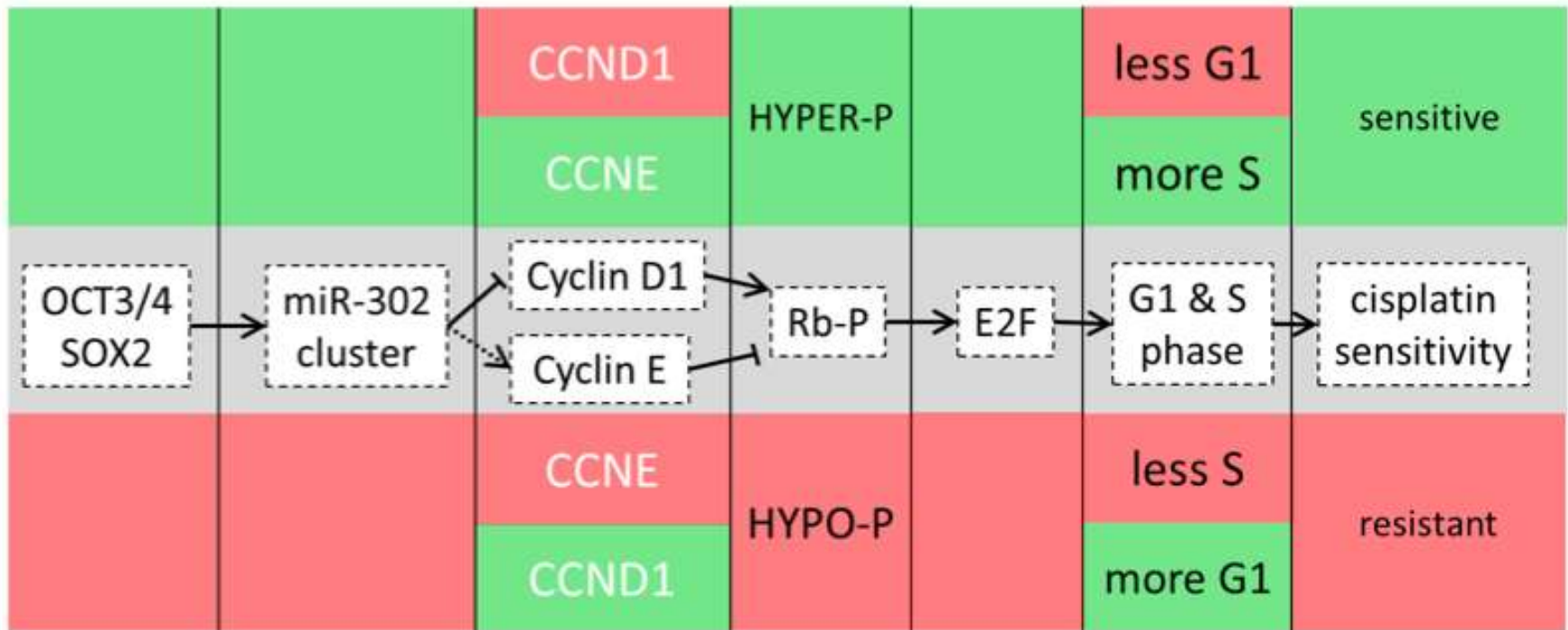
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miR-20a	UAAAGUGCUUAUAGUGCAGGUAG
miR-20b	CAAAGUGCUCAUAGUGCAGGUA
miR-93	CAAAGUGCUGUUCGUGCAGGUAG
miR-106a	CAAAGUGCUAACAGUGCAGGUA
miR-291a-3p	AAAGUGC <u>U</u> UCCACU <u>U</u> UGUGUGCC
miR-291b-3p	AAAGUGC <u>A</u> UCCA <u>U</u> UUUGU <u>U</u> UGUC
miR-294	AAAGUGC <u>U</u> UCC <u>U</u> UUUGUGUGU
miR-295	AAAGUGC <u>A</u> CUACU <u>U</u> UUUGAGUCU
miR-302b	UAAGUGC <u>U</u> UCCAUG <u>U</u> UUUAGUAG
miR-302c	CAAGUGC <u>U</u> UCCAUG <u>U</u> UUCAGUGG
miR-302d	UAAGUGC <u>U</u> UCCAUG <u>U</u> UUGAGUGU



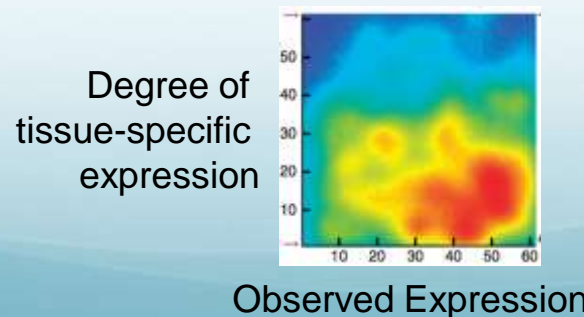
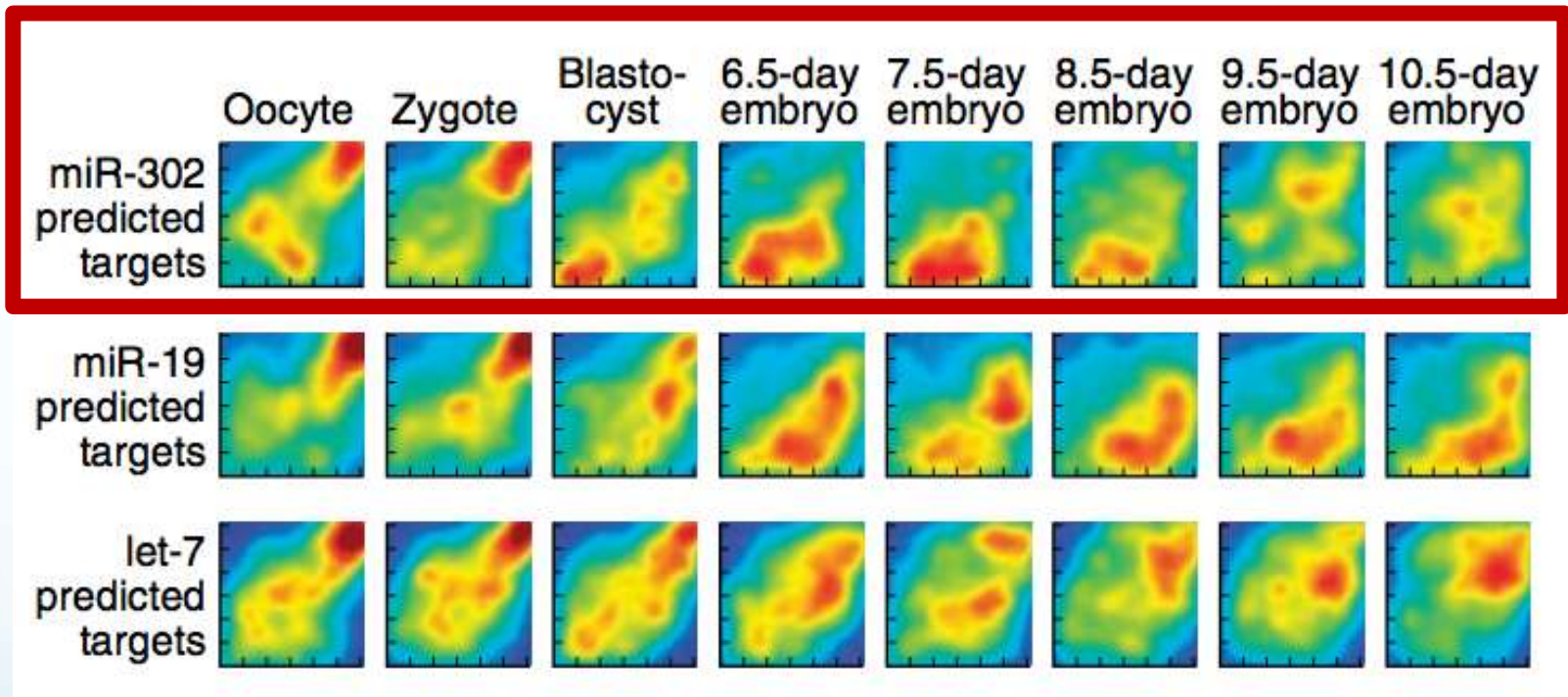
... by blocking the Cyclin D1 and allowing a faster G₁ / S transition

ES cell like



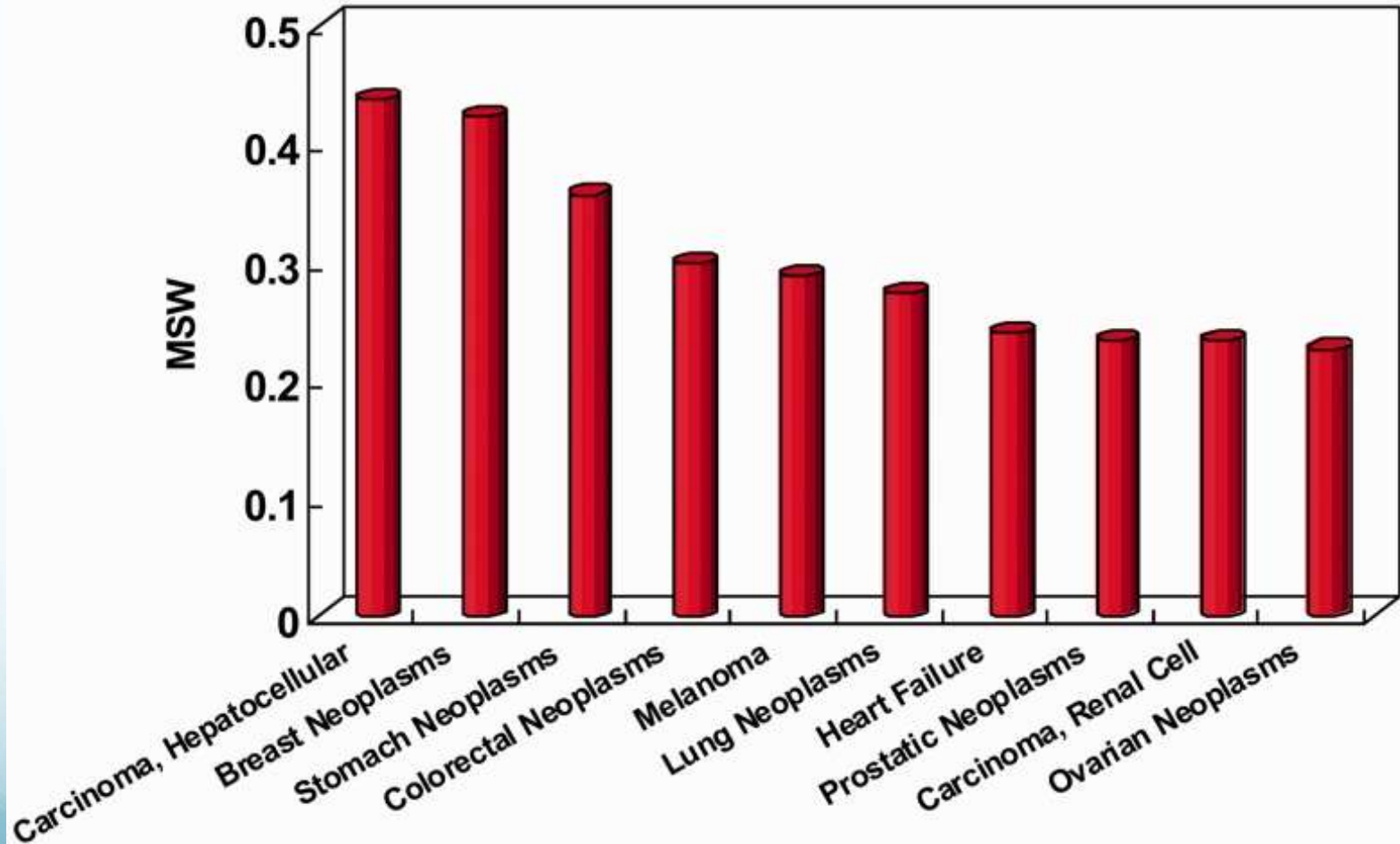
Differentiated cells

miR-302 cluster is associated with clearance of maternal transcripts

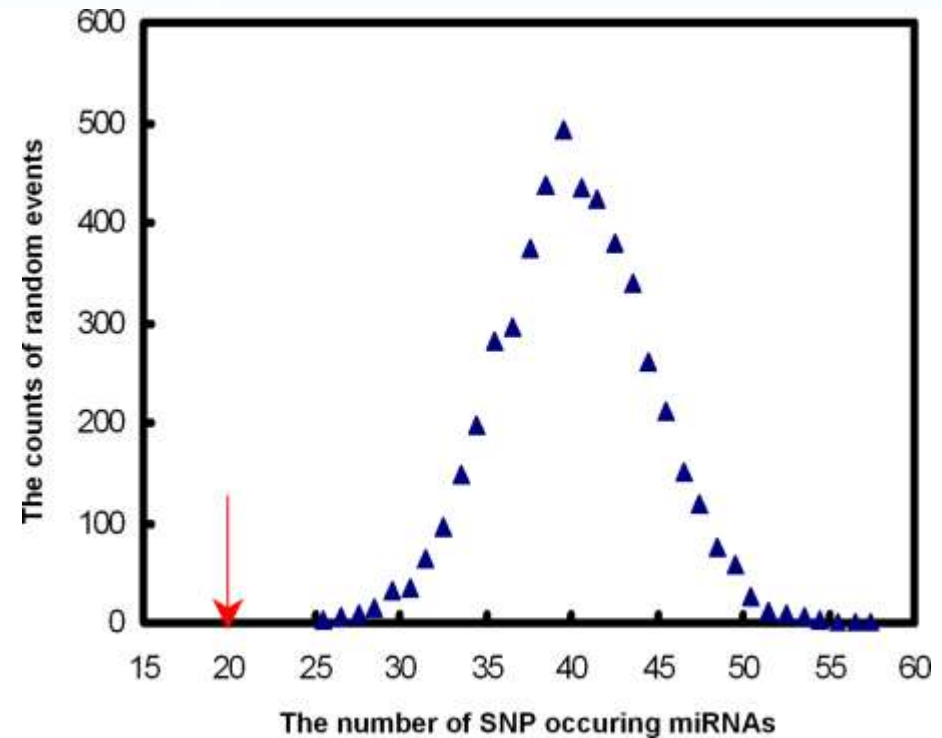
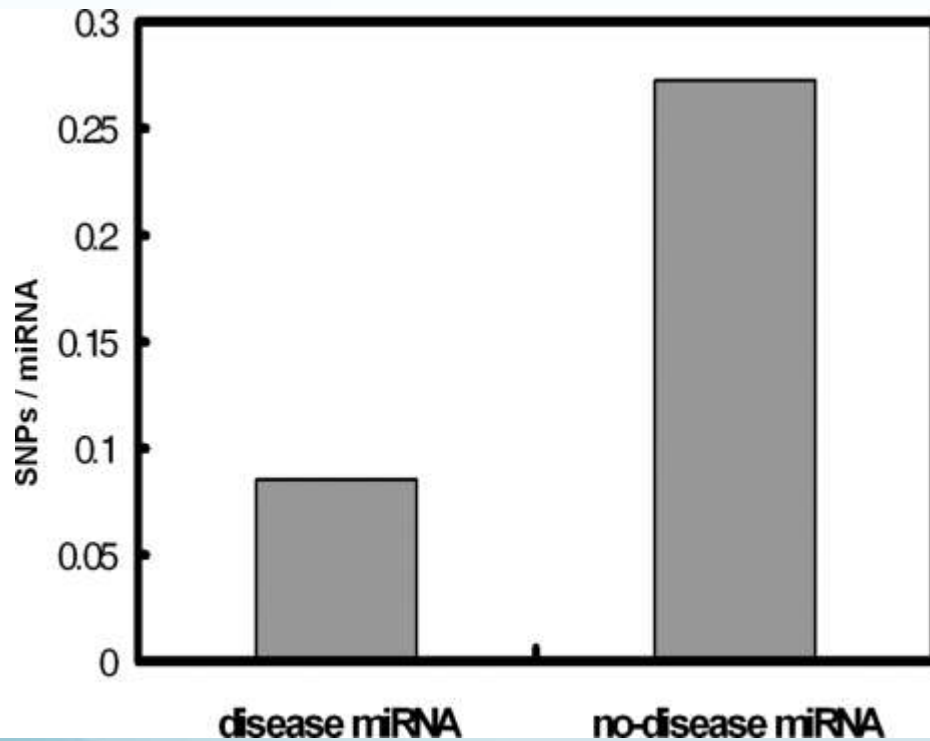


miRNA and disease

miRNA and disease



Disease-associated miRNAs are depleted for SNPs



Summary

- miRNAs exert their function through base-pairing with complementary sequence of mRNA
 - Specific function can depend on affinity / degree of base-pairing
- miRNAs have key roles in embryogenesis, both in regulation of embryogenesis genes as well as clearance of maternal mRNAs
- Misregulation of miRNAs have been implicated in a variety of diseases
 - specific mechanisms are still unclear in many cases

Thank you!

- Questions?