BIBM 2010 Tutorial:
Epigenomics and Cancer

PART 3.3:
MicroRNA and Cancer

Dec 18, 2010

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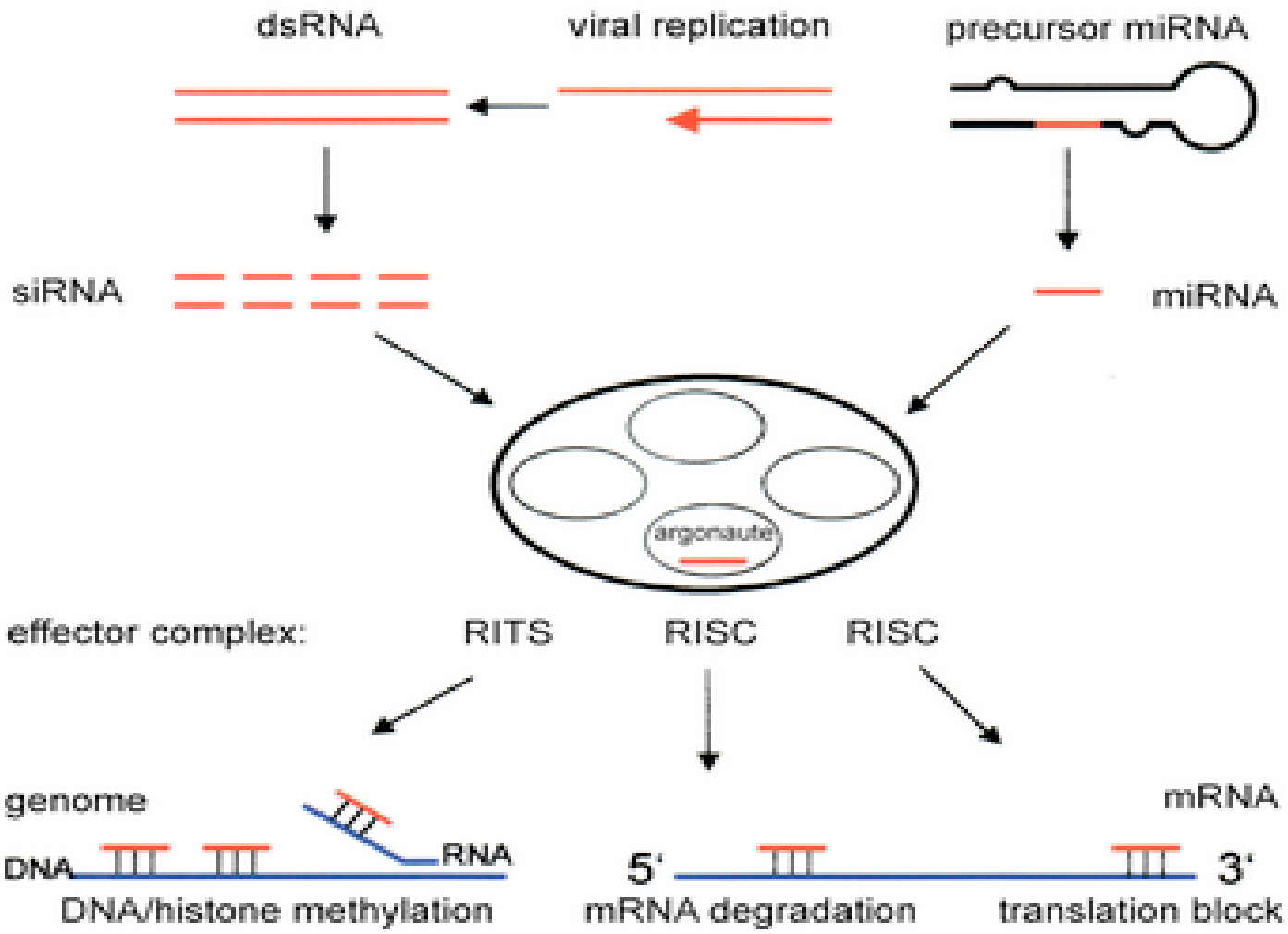
Outline of Part 3.3

- Background on microRNA
- Role of microRNA in cancer
- MicroRNA pathway and cancer

microRNA interference with genes



http://en.wikipedia.org/wiki/RNA_interference

Roles of MicroRNA in Cancer

- MicroRNAs as oncogenes
- MicroRNAs as tumor suppressors
- MicroRNAs as modulators of tumor progression and metastasis
- Global deregulation of microRNAs in cancer

Ventura and Jacks, Cell. 2009 Feb 20;136(4):586-91

MicroRNAs as oncogenes

- Ectopic expression of miR-155 in the bone marrow of mice has been reported to induce either polyclonal pre-B cell proliferation followed by full-blown B cell leukemia (Costinean et al., 2006) or myeloproliferation (O'Connell et al., 2008), depending on the system used to drive expression of the transgene.
- He et al. (2005) demonstrated that a truncated version of the miR-17~92cluster (lacking the most distal miRNA, miR-92) could cooperate with c-Myc and greatly accelerate tumorigenesis in a mouse model of B cell lymphoma.

MicroRNAs as tumor suppressors

- miR- 15a~16-1 is located in the minimally deleted tumor suppressor gene region on 13q14 in CLL (Calin et al., 2002). Also more than 50% of human prostate cancers carry a deletion of 13q14.
- The human genome contains a dozen let-7 family members, organized in eight different loci. Reduced expression of multiple members of the let-7 family is frequently observed in lung cancers.

MicroRNAs as modulators of tumor progression and metastasis

- The miR-10b miRNA is a direct transcriptional target of Twist1, a known inducer of the epithelial-to-mesenchymal transition (EMT) and metastatic progression.
- Members of the miR-200 family of miRNAs target the ZEB transcription factors, known inducers of the EMT, and thus reduce cellular migration and invasiveness

Global deregulation of microRNAs in cancer

- miRNA expression profiling experiments have demonstrated that most (although not all) miRNAs are underexpressed in tumor tissues compared to normal tissues (Lu et al., 2005).
- In general, more genes are expressed in cancer cells than in normal cells, which is consistent with a global deregulation of microRNAs.
- However, we need to look at the expression levels of individual microRNAs.
- For example, high expression of miR-155 and low expression of let-7 correlate with poor prognosis (Yanaihara et al., 2006).

miRNA genomic and functional organization (J Pathol. 2011 Jan;223(2):102-15)

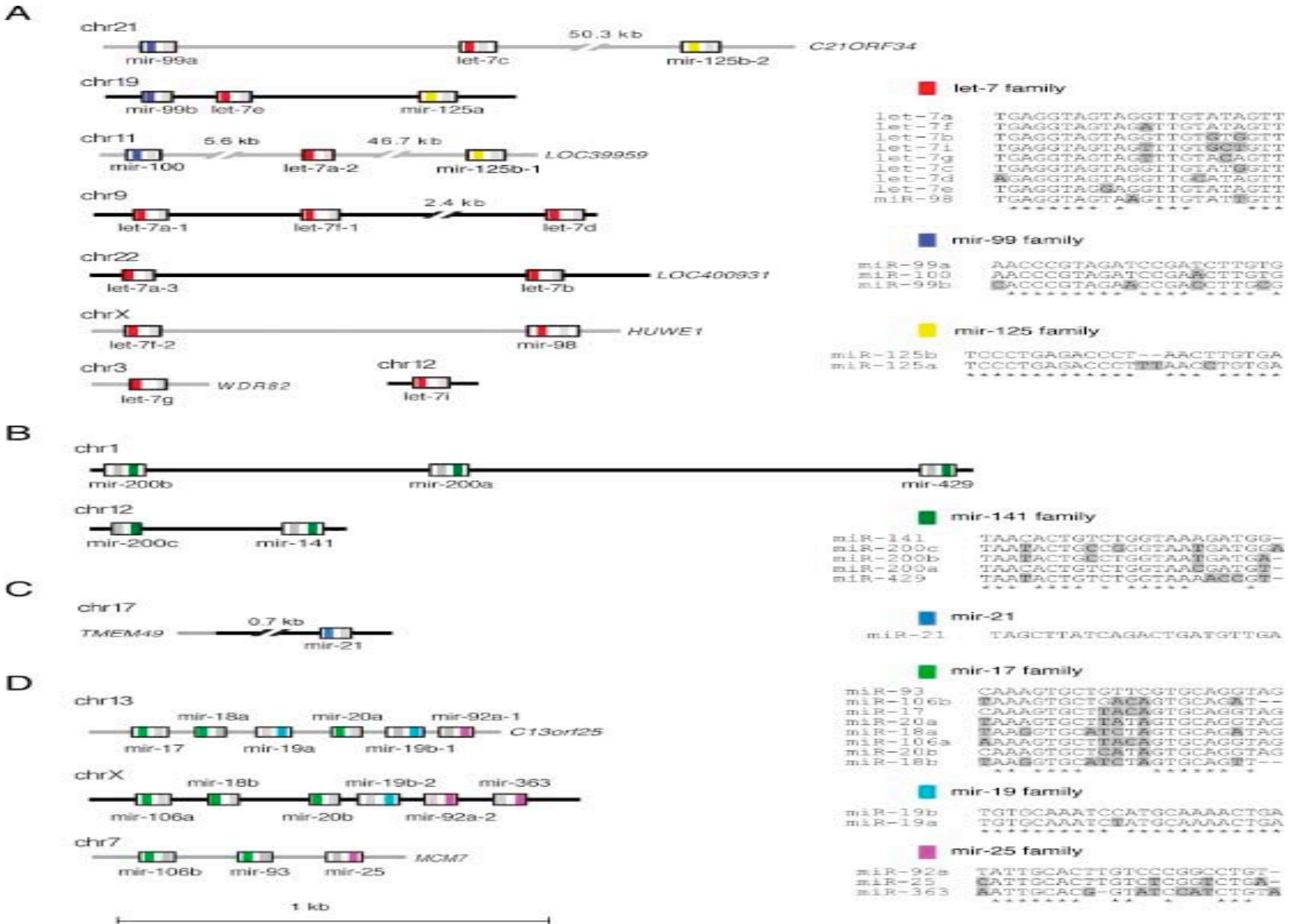


Table 1. MicroRNAs and Cancer

Mutation/Epigenetic Change	Predicted Functional Consequence	Examples
Deletion of miRNA	Derepression of oncogene	*miR-15a-16-1*
Epigenetic silencing of miRNA locus	Derepression of oncogene	*miR-29*, *miR-203*
Point mutation affecting an miRNA or an miRNA precursor	Reduced affinity for oncogene	*N.E.*
	Increased affinity for tumor suppressor gene	*N.E.*
	Reduced processing efficiency	*miR-15a~16-1**
	Increased processing efficiency	*N.E.*
Genomic amplification or translocation of miRNA locus	Increased repression of tumor suppressor gene	*miR-17~92*, *miR-21*
Loss of epigenetic silencing of miRNA locus	Increased repression of target tumor suppressor gene	*N.E.*
Point mutation in oncogene	Decreased or lost affinity for miRNA	*N.E.*
Point mutation in tumor suppressor gene	Gain or increased affinity for miRNA	*N.E.*
Rearrangement of 3′UTR (translocation, deletion)	Loss of miRNA-mediated repression	*HMGA-2*
	Gain of miRNA-mediated repression	*N.E.*

Shown are potentially oncogenic genetic and epigenetic changes involving miRNAs or their targets. The table includes changes affecting the miRNA gene directly as well as genetic lesions in protein-coding oncogenes and tumor suppressor genes that result in reduced or increased affinity for one or more miRNAs. (N.E., no known examples; *, the mutation is a single base change in *pri-miR-15a~16-1*, immediately downstream of the *pre-miR-16-1* sequence, and the sequence of the mature miRNA is not affected.)

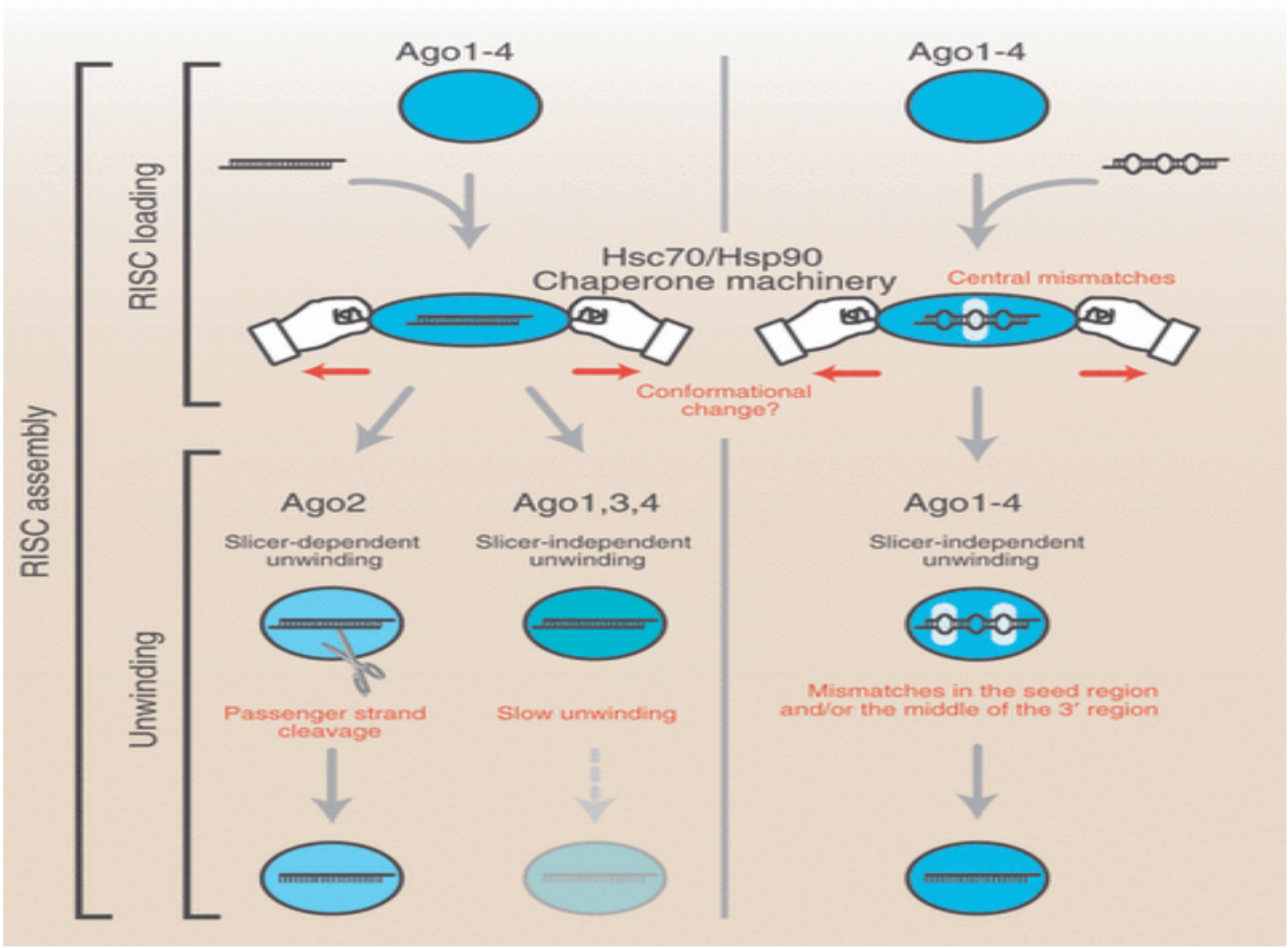
Ventura and Jacks, Cell. 2009 Feb 20;136(4):586-91

MiroRNA Pathway and Cancer

Kwak et al, Cancer Science 2010

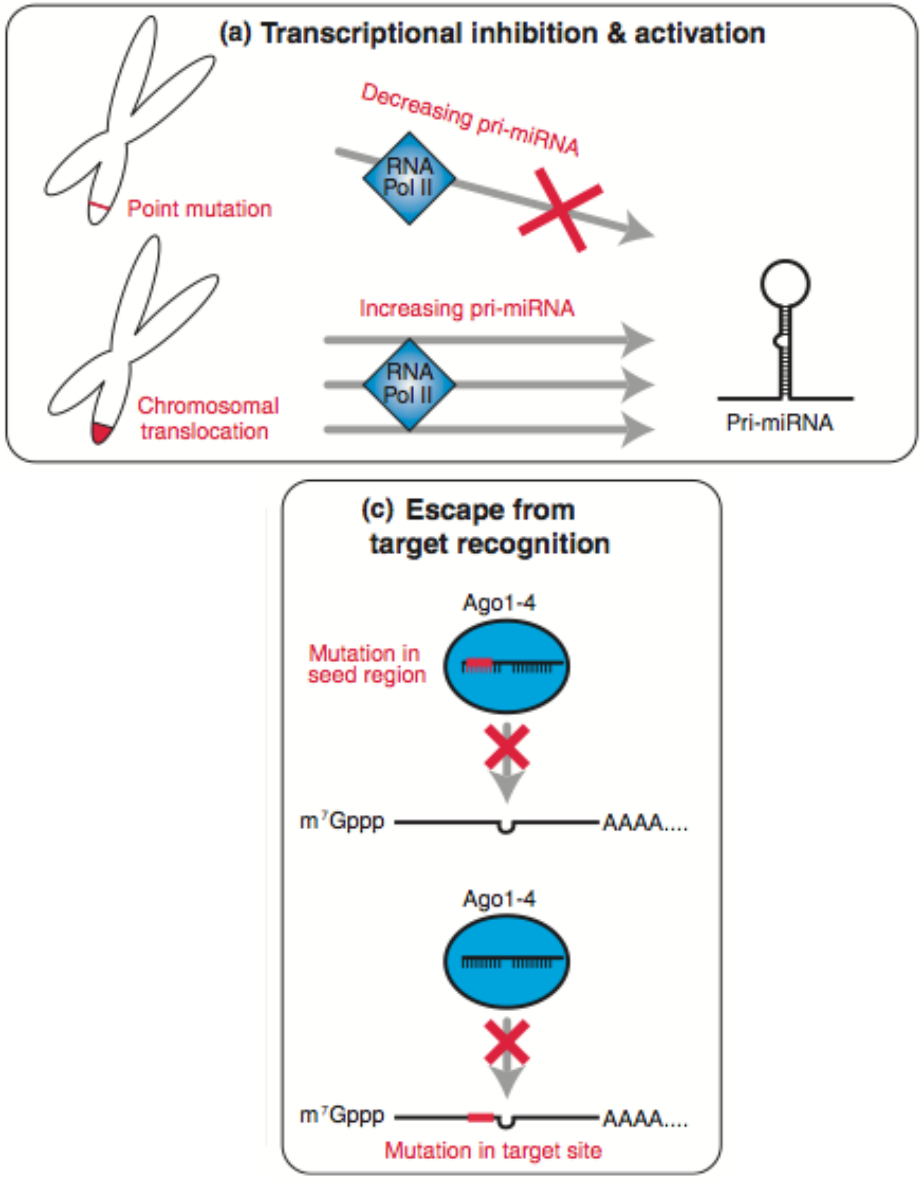
- Genomic abnormalities
- Transcriptional activation
- Dysregulation of the miroRNA pathway

RNA-induced silencing complex (RISC) assembly



Kwak et al, Cancer Science 2010

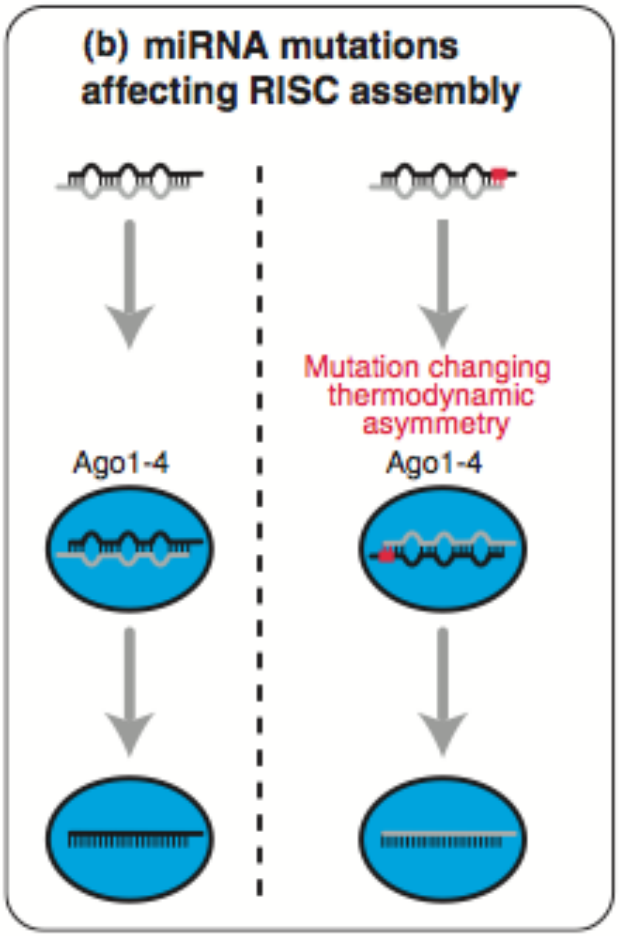
Genomic Abnormalities



- Genomic abnormalities, such as chromosomal translocations and point mutations, can attenuate or stimulate miRNA transcription leading to an increase or decrease of primary miRNA (Fig 4a)
- Point mutations within miRNAs or their flanking regions can lead to altered transcription levels (Fig 4a)
- Point mutations in miRNA binding sites of target mRNA can compromise the ability to silence target mRNA transcriptions (Fig 4c).

Kwak et al, Cancer Science 2010

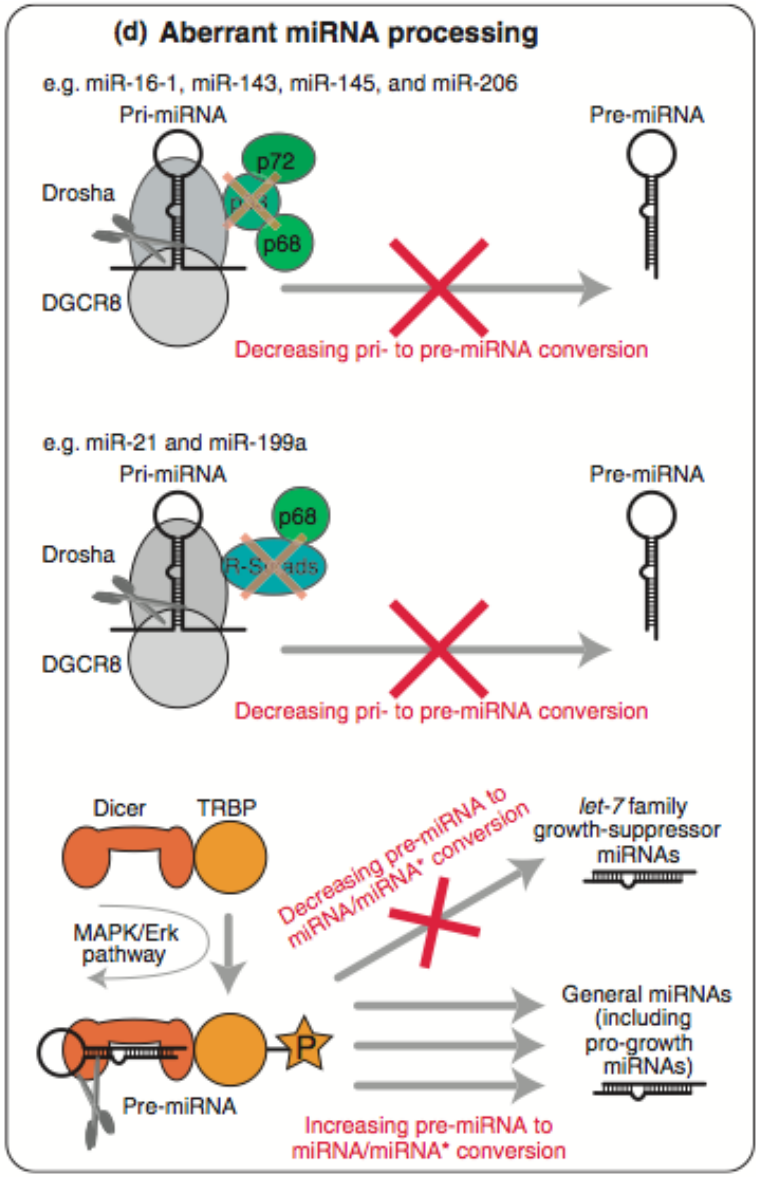
Mutations in a miRNA gene



- (b) Mutations in a miRNA gene can lead to RNA-induced silencing (RISC) assembly abnormalities. For example, when nucleotides that establish the thermodynamic asymmetry are substituted, this can lead to “flipped” strand selection, resulting in the miRNA* strand, instead of the miRNA strand, being favored for RISC incorporation

Kwak et al, Cancer Science 2010

MicroRNA (miRNA) pathway and cancer



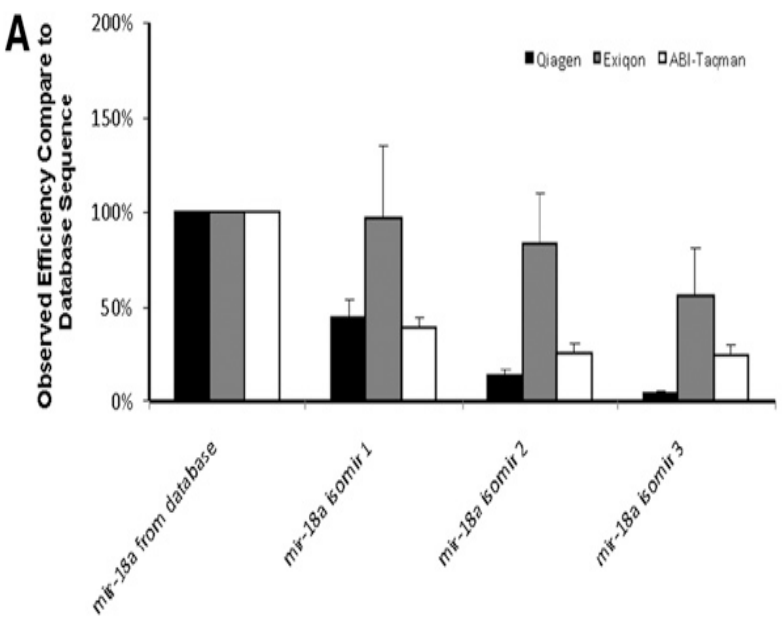
- Genomic abnormalities can also result in aberrant miRNA processing. Some pri-miRNAs require additional proteins for efficient conversion. p53 mutants affect the interaction between p68/p72 RNA helicases and Drosha and this decreases pri- to precursor miRNA (pre-miRNA) conversion of a subset of miRNAs.
- Additionally, p68 associates with receptor-regulated Smads. This interaction has been shown to be important for efficient pri- to pre-miRNA conversion of another subset of miRNAs.
- In the cytoplasm, TAR RNA-binding protein (TRBP) is phosphorylated by MAPK/Erk signaling. The phosphorylation of TRBP increases pre-miRNA to miRNA/miRNA* conversion for general miRNAs, but it decreases conversion for *let-7* family miRNAs. AAA..., poly(A) tail; Ago, Argonaute; DGCR8, DiGeorge syndrome critical region 8 protein.

Kwak et al, Cancer Science 2010

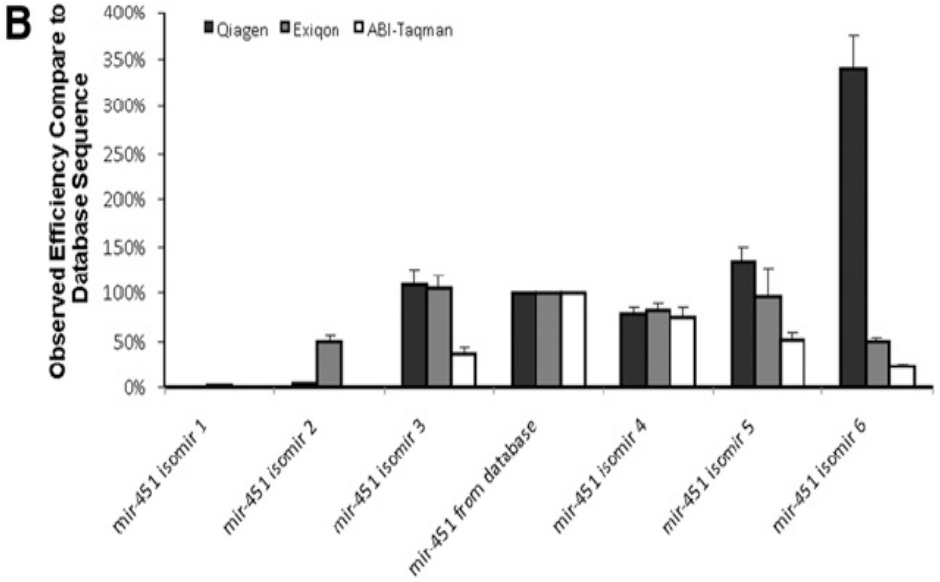
Complexity of the microRNA repertoire revealed by next-generation sequencing. RNA. 2010 Nov;16(11):2170-80.

- It has been shown that some miRNAs frequently have **sequence variations** termed **isomirs**.
- we conducted a comprehensive survey of **miRNA sequence variations** from human and mouse samples using next generation sequencing platforms.
- Our results suggest that the process of generating this isomir spectrum might not be random and **that heterogeneity at the ends of miRNA affects the consistency and accuracy of miRNA level measurement.**
- we have constructed **a database from our sequencing data** that catalogs the entire repertoire of miRNA sequences (http://galas.systemsbiology.net/cgi-bin/isomir/find.pl)

Isomirs: Character Variations in Target Sequences



mir-18a from database	TAAGGTGCATCTAGTGCAGATAG
mir-18a isomir 1	AAGGTGCATCTAGTGCAGATA
mir-18a isomir 2	GGTGCATCTAGTGCAGATA
mir-18a isomir 3	GTGCATCTAGTGCAGATA



mir-451 isomir 1	AAACCGTTACCATTACTGA
mir-451 isomir 2	AAACCGTTACCATTACTGAG
mir-451 isomir 3	AAACCGTTACCATTACTGAGT
mir-451 from database	AAACCGTTACCATTACTGAGTT
mir-451 isomir 4	AAACCGTTACCATTACTGAGTTT
mir-451 isomir 5	AAACCGTTACCATTACTGAGTTTA
mir-451 isomir 6	AAACCGTTACCATTACTGAGTTTAG

Character variations at the 3' end show bigger variations of expression levels (B) than variations at the 5' end (A), measured by three different qPCR methods.

Complexity of the microRNA repertoire revealed by next-generation sequencing, RNA. 2010 Nov;16(11):2170-80

References for MicroRNA vs. Cancer

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