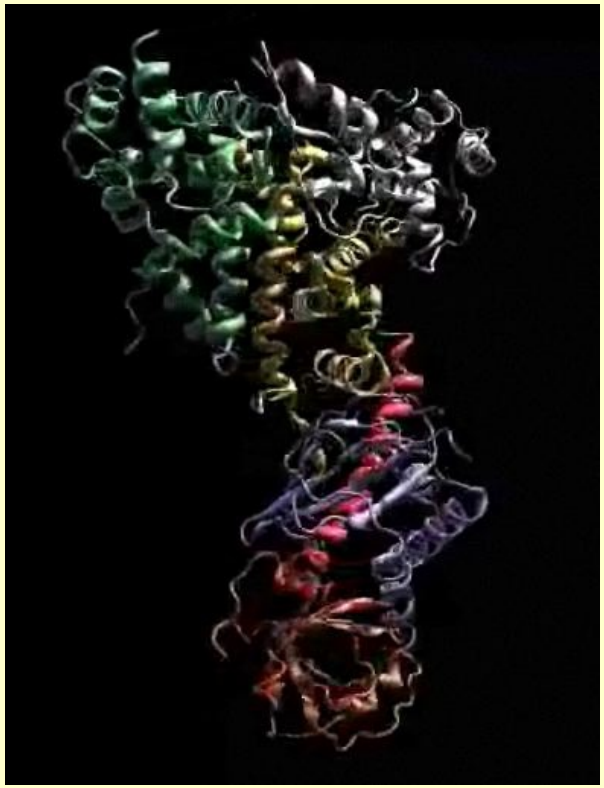
Your Genes and Your Health

http://bio84.stanford.edu/

miRNA Regulatory Networks

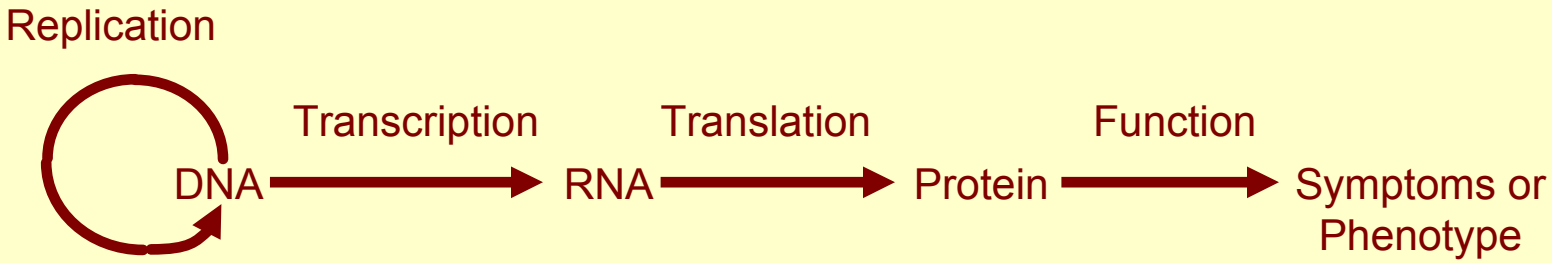


Doug Brutlag, Professor Emeritus
Biochemistry & Medicine
Stanford University School of Medicine

Announcements

- For those of you taking the course for Credit or for a Letter Grade:
  - Your 1-2 page paper for credit or a 4-5 page paper for a letter grade will be due March 16 by 7:00 PM (the time of last class).
  - Possible homework topics are on the course web site
  - http://bio84.stanford.edu/
  - You must send me your paper as an email or email attachment to brutlag@stanford.edu.
  - I do not accept hardcopy"papers".

Steps in Gene Expression

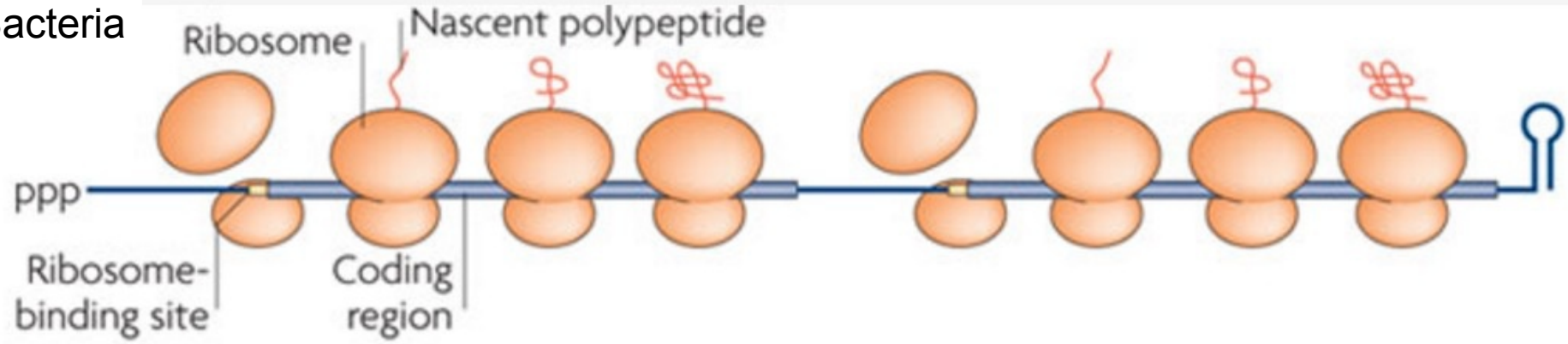


Gene Regulatory Mechanisms

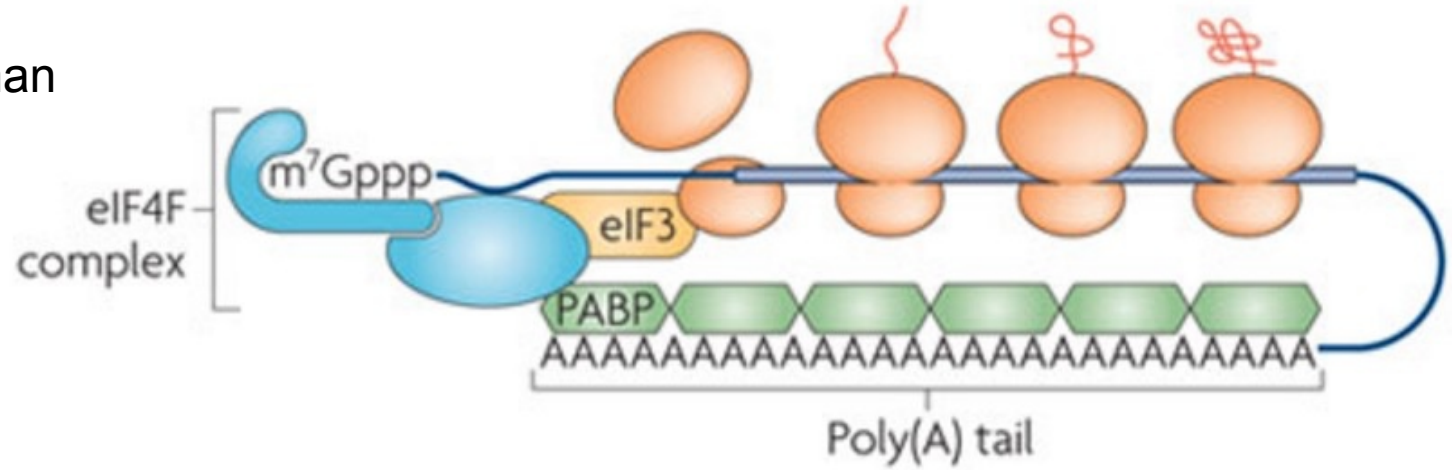
- Transcriptional Mechanisms
  - Type of promoters & RNA polymerase
  - Control of Transcription
  - Transcription Factors and TFBS
- RNA processing
  - Capping
  - Splicing and Alternative Splicing
  - Poly-Adenylation
- Translational Mechanisms
  - Micro RNAs (miRNAs) inhibit translation
  - Silencer RNAs (siRNAs or RNAi) degrading mRNA
- Epigenetic Mechanisms
  - DNA methylation
  - Histone modifications
  - Chromatin remodeling

Mechanism of Translation Mediated by Ribosomes

Bacteria



Human

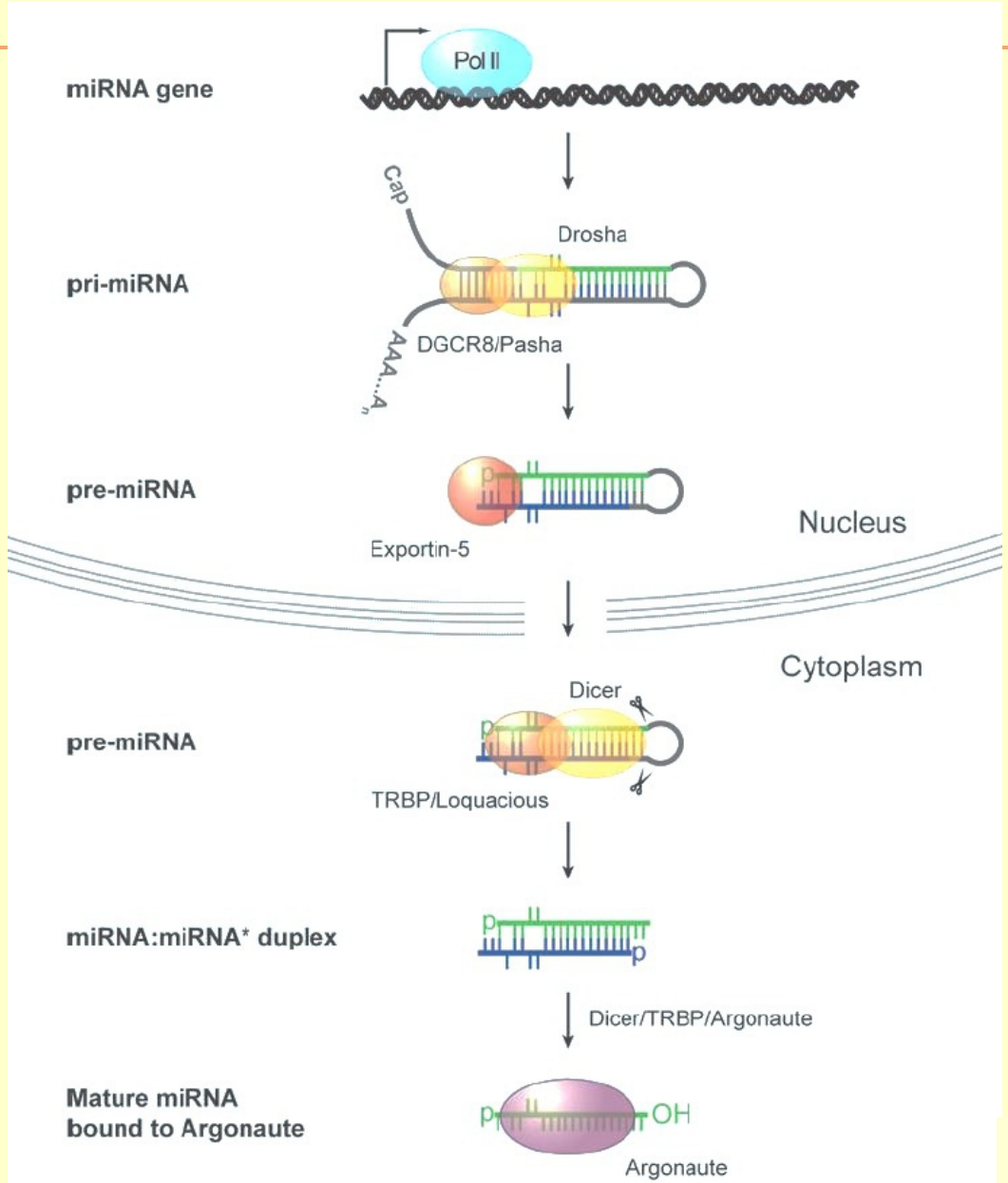


Belasco, Nature Reviews Molecular Cell Biology 11, 467-478 (July 2010)

Regulation of Translation by microRNAs

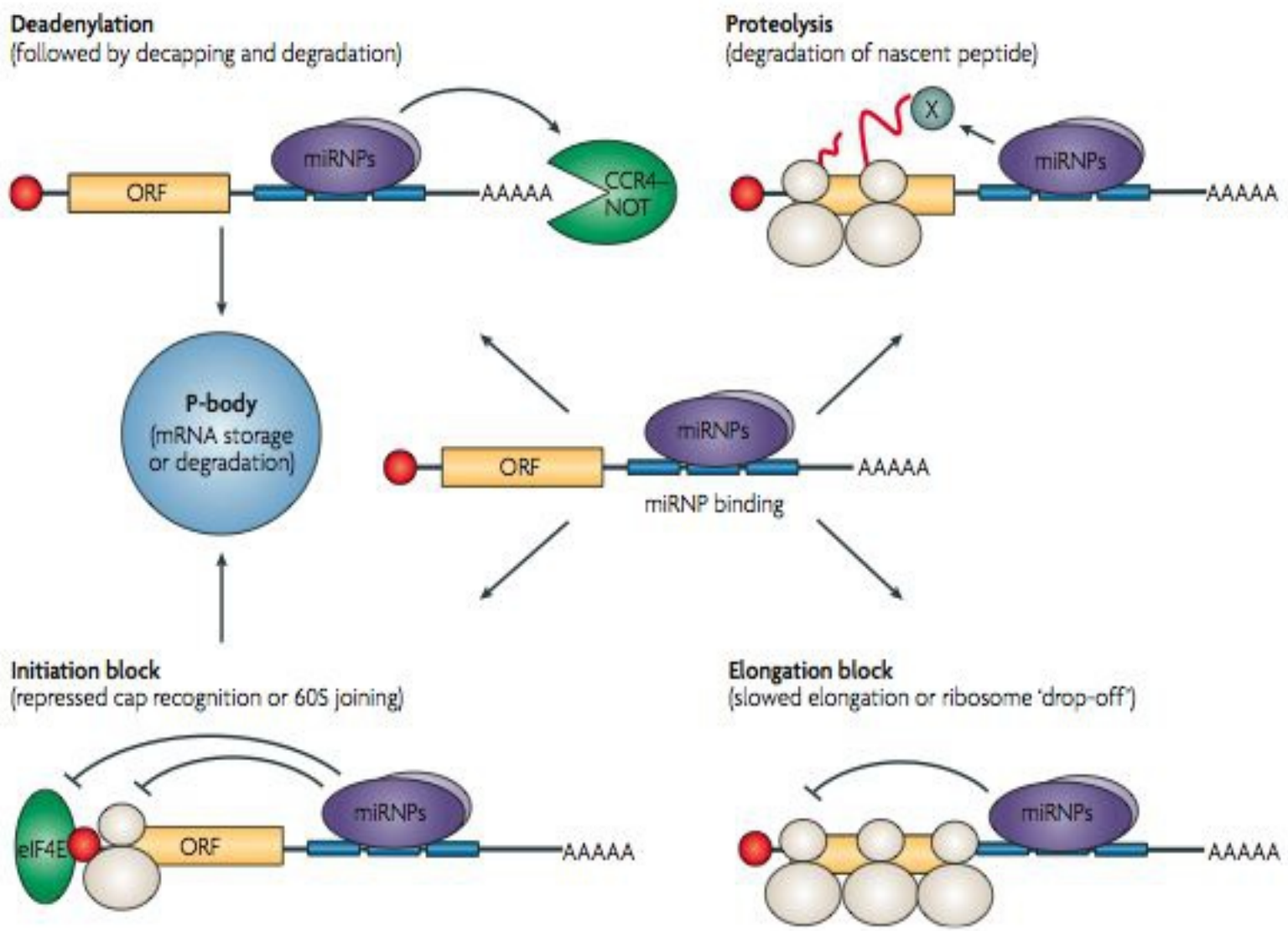
- MicroRNAs can inhibit translation of mRNAs and cause degradation of mRNAs
- Micro RNAs form an RNA-Induced Silencing Complex (RISC) that can both inhibit translation and degrade mRNA
- MicroRNA RISC complexes bind to the 3′ UTR regions of mRNAs and stop translation and induce mRNA degradation

microRNA Biogenesis

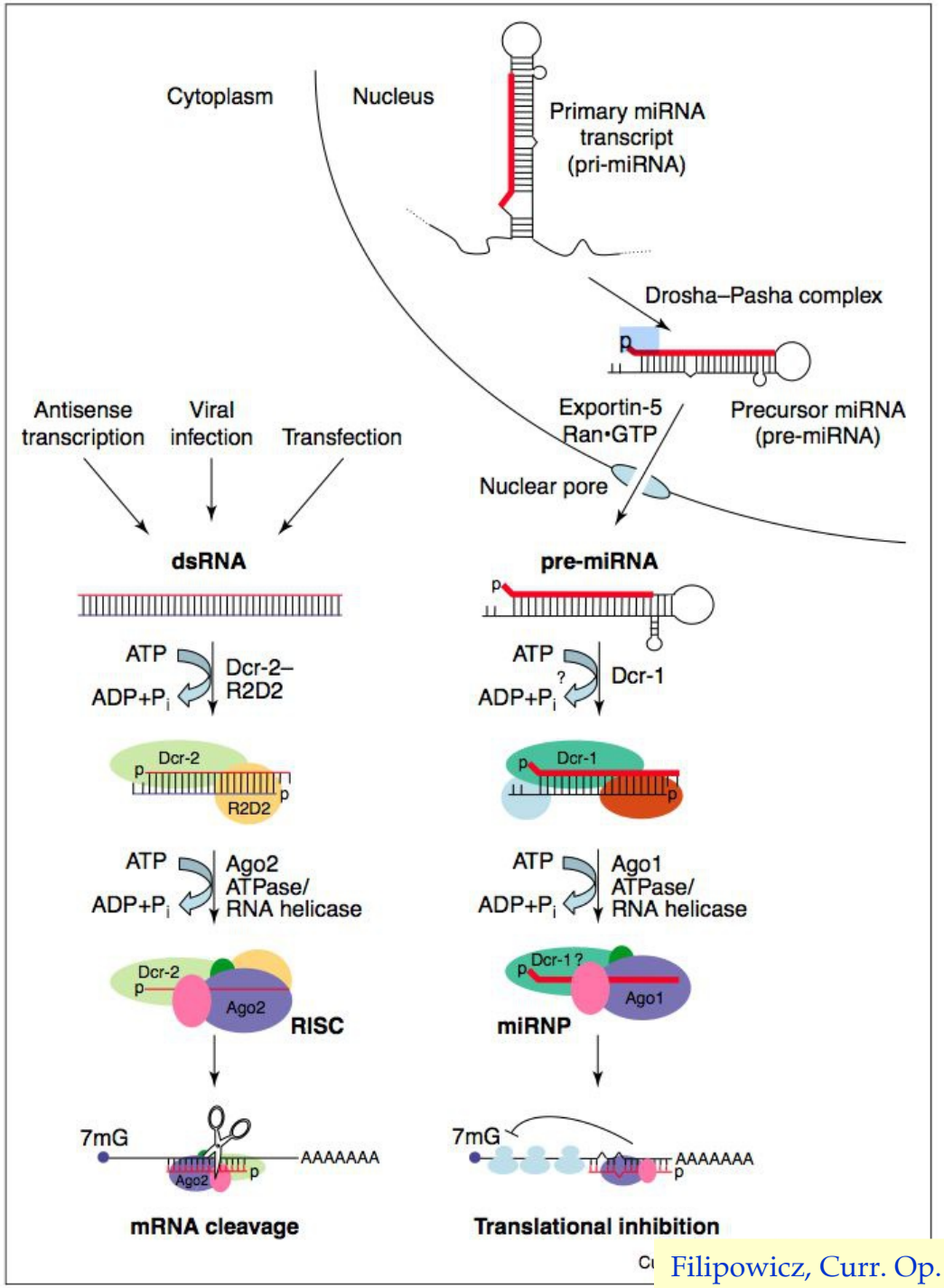


Annu. Rev. Cell Dev. Biol. 2007.23:175-205

Mechanisms of Translational Regulation by miRNP Complexes



Filipowicz (2008) Nature Review Genetics 9:102-112.



siRNA mediated degradation of mRNA

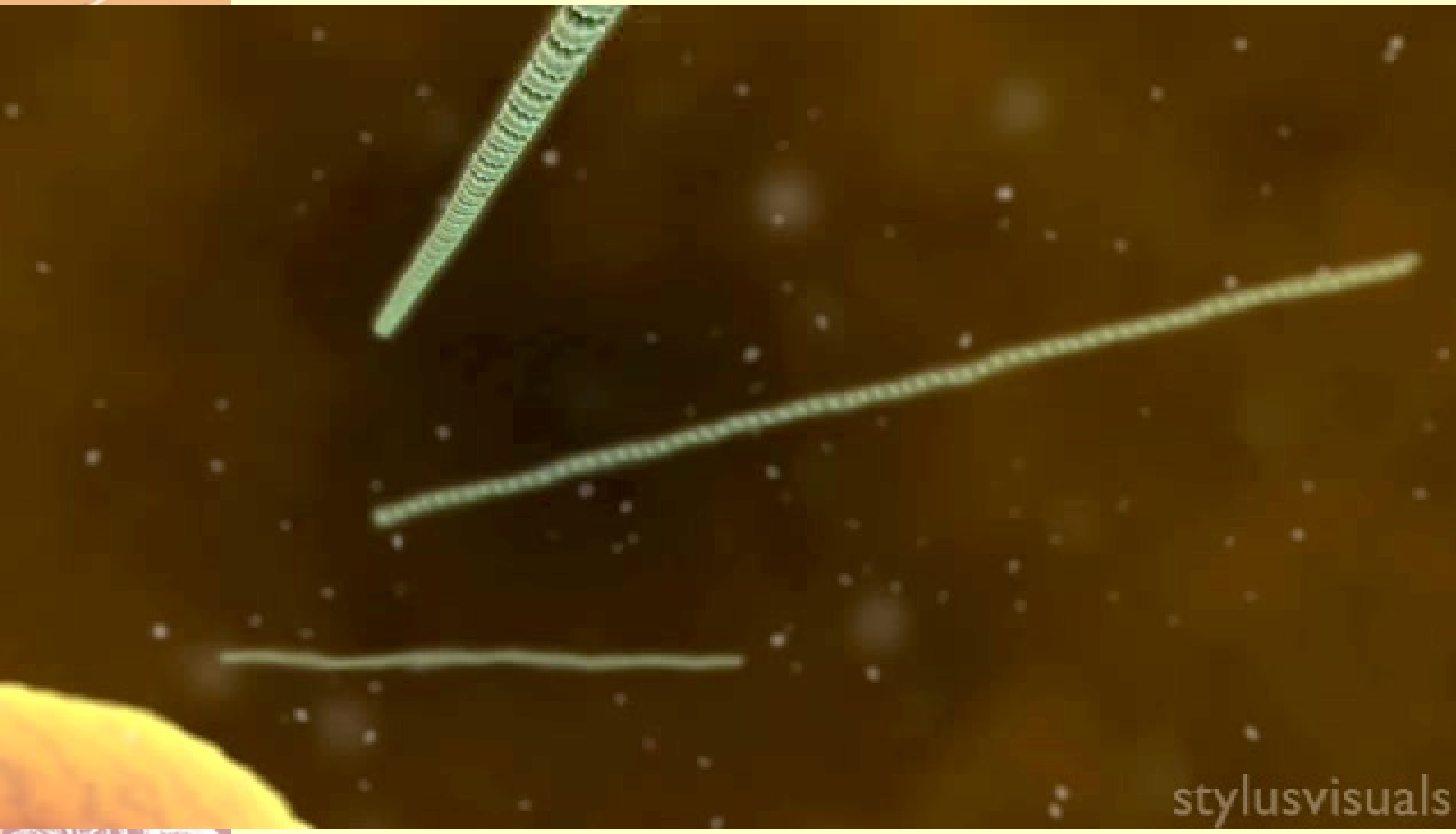
versus

miRNA mediated inhibition of mRNA translation

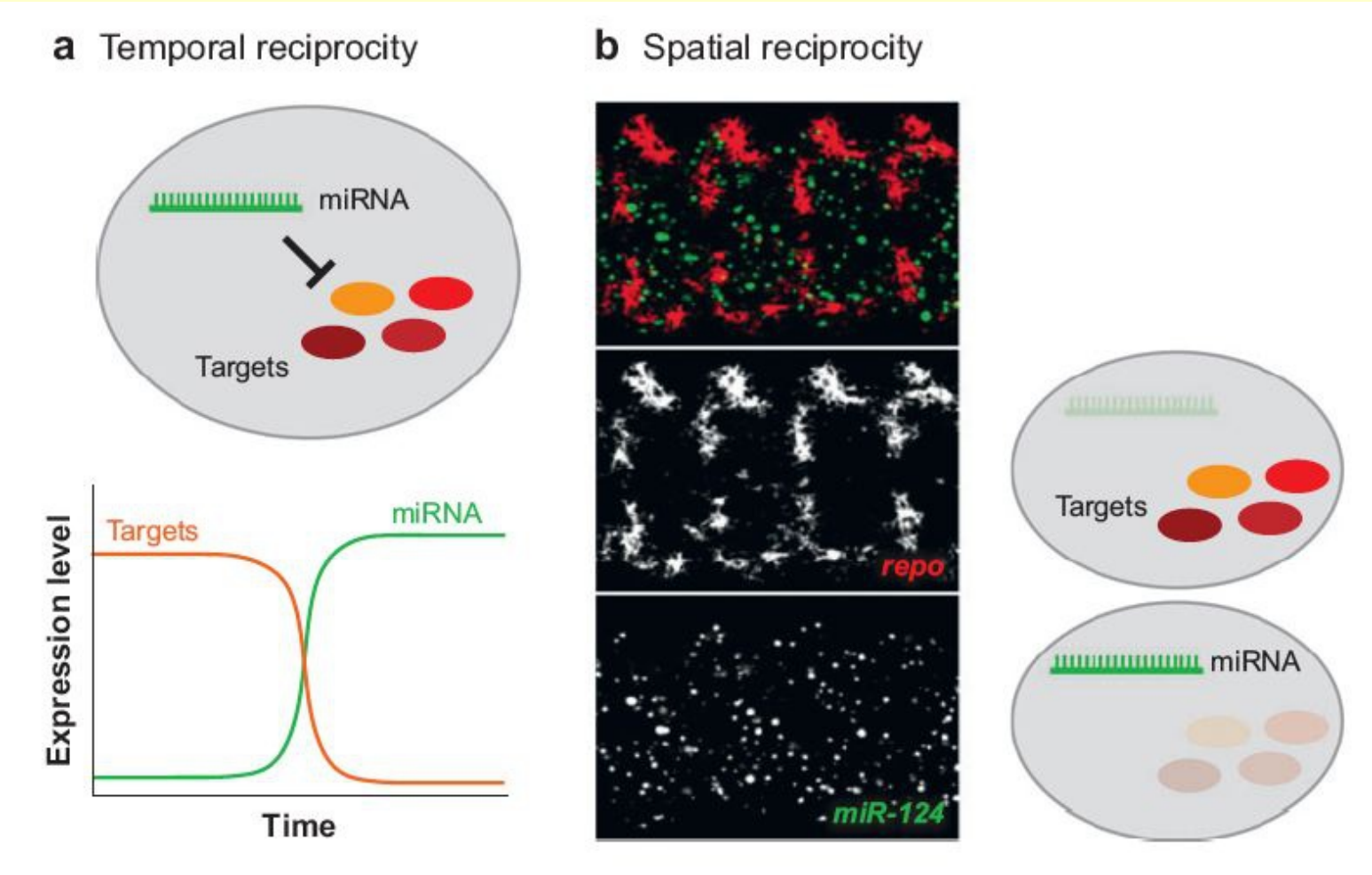
Filipowicz, Curr. Op. Structural Biology 15: 331-341 (2005)

Dicer Mechanism

(New York Museum of Modern Art - MOMA)

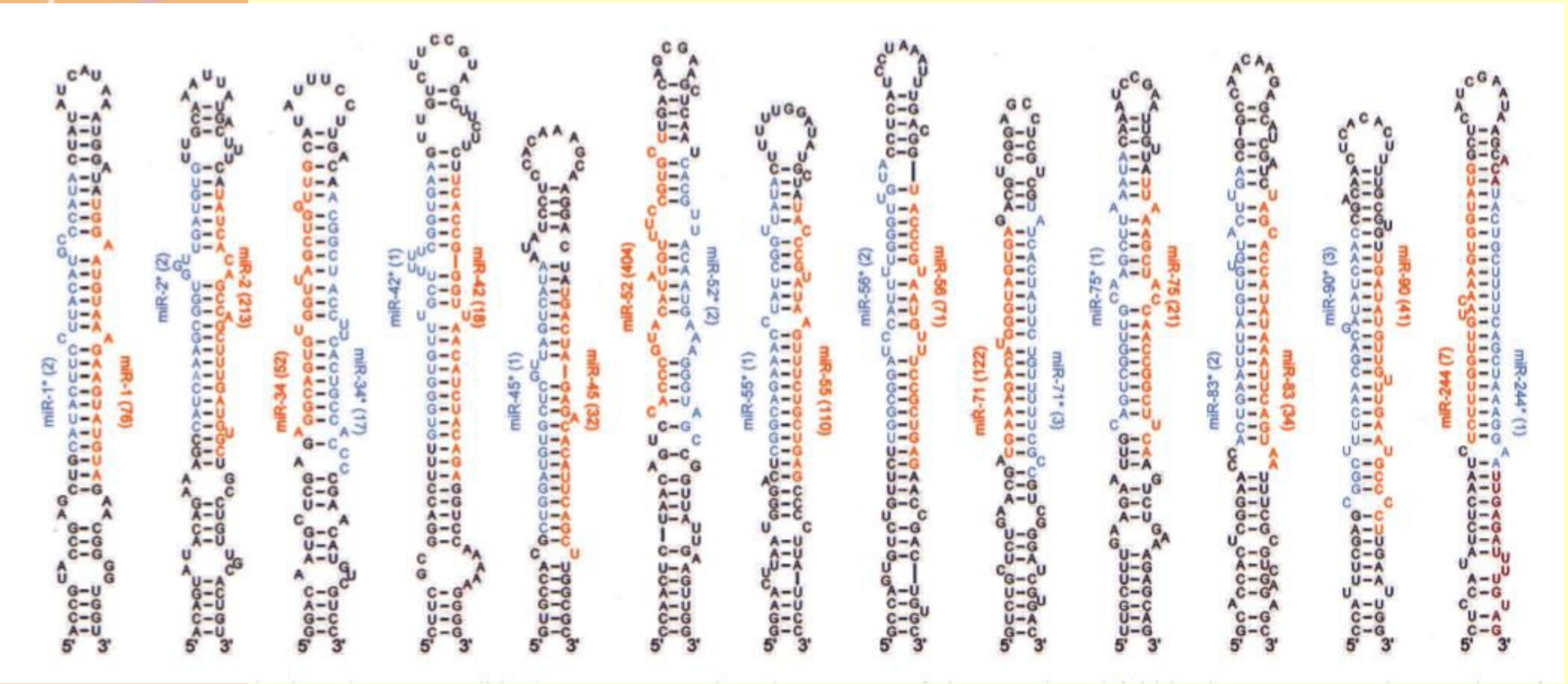


miRNA Expression Results in Temporal and Spatial Reciprocity with Target Expression



Annu. Rev. Cell Dev. Biol. 2007.23:175-205

Predicted miRNA Precursors



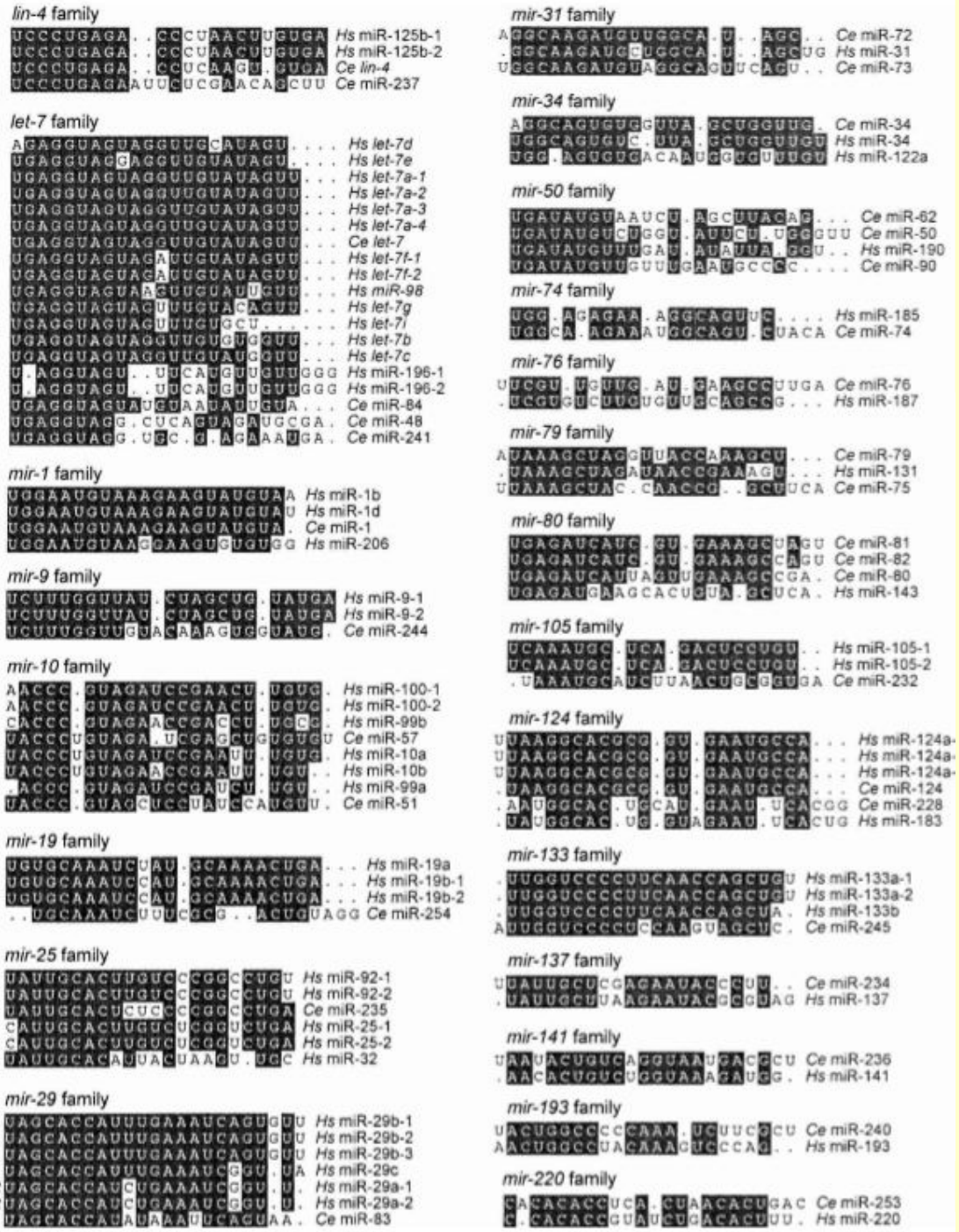
Human miRNAs (March 9, 2016)

- Total number of miRNAs known 28,645
- Number human miRNAs identified 2,661
- Number of human mRNA targets 34,788

- Each miRNA can have multiple mRNA targets (13 on average)
- Each mRNA can have multiple miRNA binding sites (each mRNA has 2 miRNA binding sites on average)

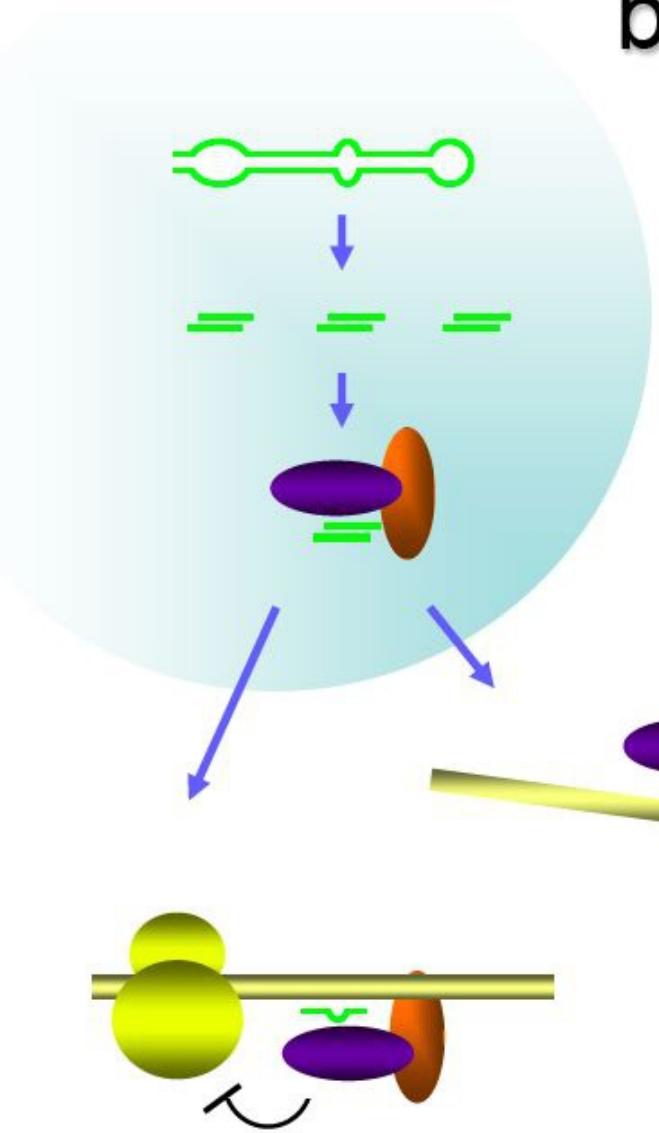
miRBase @ http://www.mirbase.org/
MicroCosm @ http://www.ebi.ac.uk/enright-srv/microcosm, u.francke.hgjc.10/9/07

Homology Between *C. elegans* and *Homo sapiens* miRNAs



Lim (2003) Genes & Dev. 17: 991-1

Thousands of microRNAs act in multiple biological events



Developmental timing

Differentiation

Aging

Apoptosis

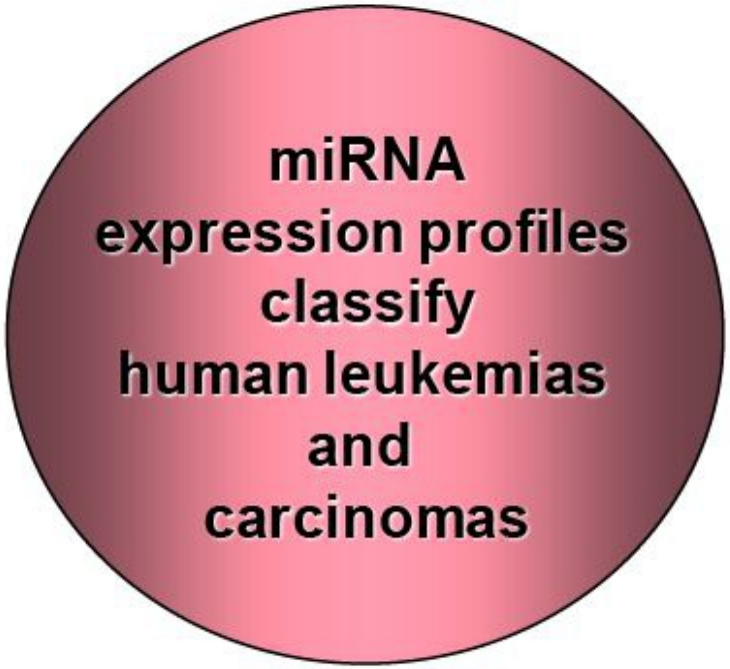
Metabolism

Cancer

…

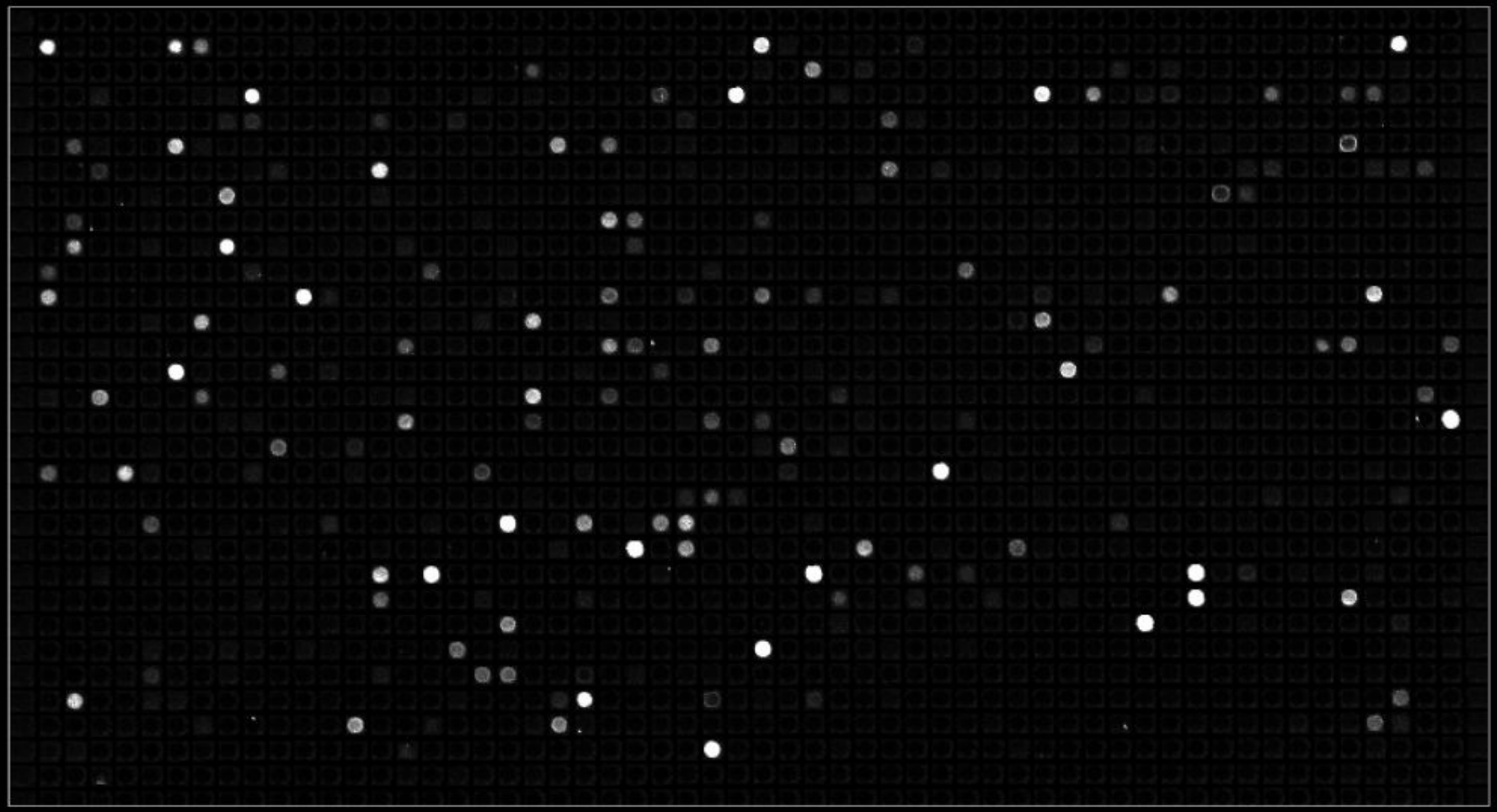
Cell fate/differentiation, Cell cycle…

ALTERATIONS OF MICRORNAS ARE FOUND IN EVERY TYPE OF HUMAN CANCER

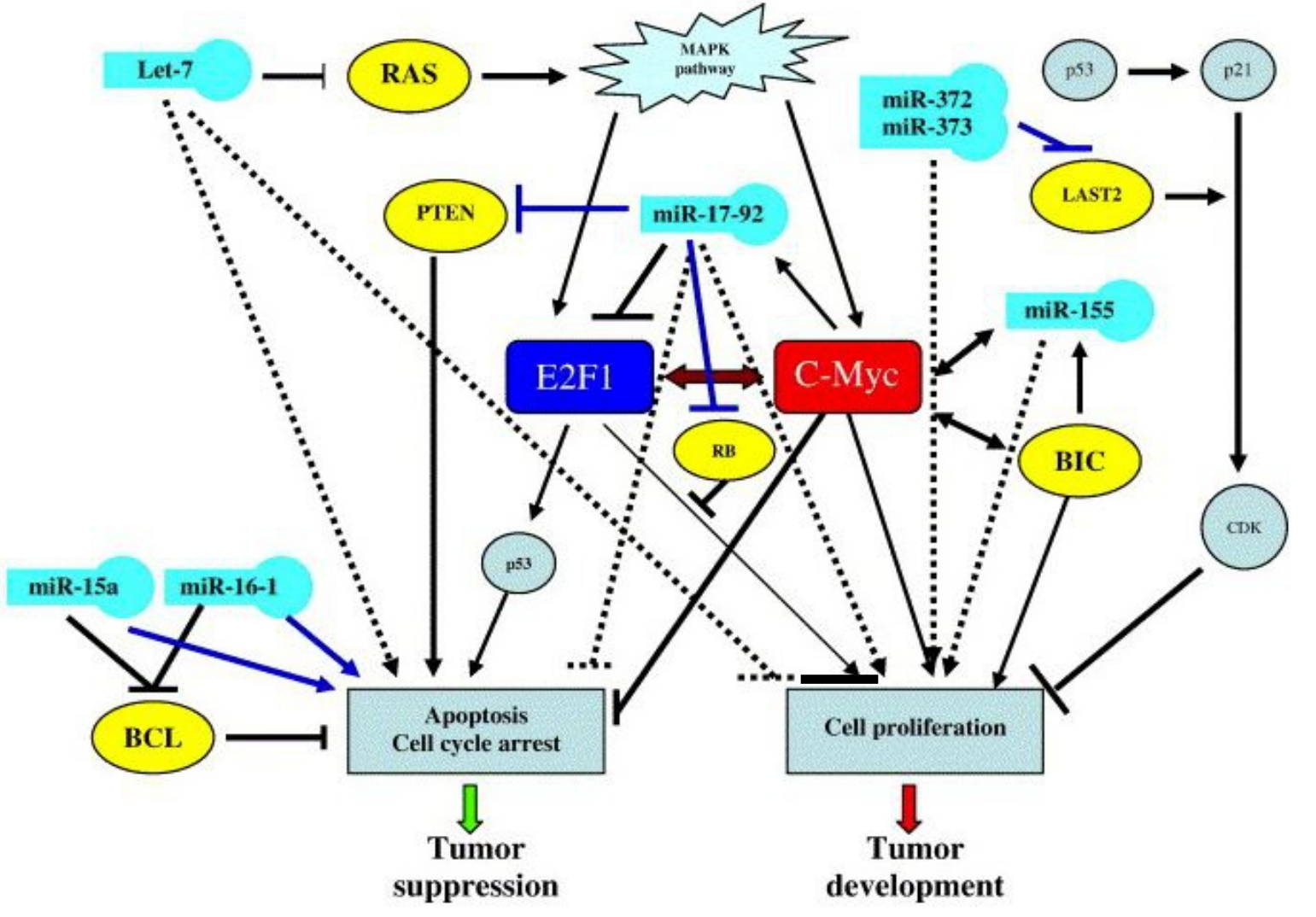


(Calin et al, PNAS 2002; Lu et al, Nature, 2005; Volinia & Calin et al, PNAS 2006; Landgraf et al, Cell 2007)

Profiling miRNA expression using custom microarrays



miRNAs as Oncogenes and Tumor Suppressors



Zhang et al Dev Biol. 2007 Feb 1;302(1):1-12

miRNAs Involved in Human Cancer

Croce Nat Rev Genet. 2009 Oct;10(10):704-14

MicroRNAs Commonly Associated with Human Cancer

miRNA	Gene Loci	Cancer association	Function*	References
miR15, miR-16	chromosome 13q14	Frequently deleted/downregulated in B-cell chronic lymphocytic leukemia. Negatively regulates the anti-apoptotic gene, BCL2.	TS	Calin, 2002 Cimmino, 2005
miR-143, miR-145	chromosome 5q3233	Decreased abundance in colorectal cancer. Down-regulated in breast, prostate, cervical, and lymphoid cancer celllines. miR-145 decreased in breast cancer.	TS	Michael, 2003 Iorio, 2005
miR-21	chromosome 17q23.2	Antiapoptotic factor. Upregulated in glioblastomas and breast cancer.	OG	Chan, 2005 Ciafre, 2005 Iorio, 2005
let-7	multiple loci	Negatively regulates the Ras oncogene. Directs cell proliferation, differentiation. Decreased abundance in lung cancer.	TS	Johnson, 2005 Takamizawa, 2004
miR-142	chromosome 17q22	t(8,17) translocation that places the MYC oncogene downstream of the *mir-142* hairpin resulting in an aggressive B cell leukemia due to MYC over-expression.	N/A	Lagos-Quintana, 2002
BIC/miR-155	chromosome 21q21	Upregulated in pediatric Burkitt's lymphomas, Hodgkins, primary mediastinal and diffuse large B cell lymphomas. Upregulated in human breast cancer.	OG	Eis, 2005 Kluiver, 2005 van den Berg, 2003 Metzler, 2003 Iorio, 2005
miR-17-19b cluster	chromosome 13q3132	Upregulated by the c-Myc oncogene Negatively modulates E2F1 oncogene. Loss-of-heterozygosity of cluste in hepatocellular carcinoma. Over-expressed in B-cell lymphomas.	TS/ OG	He, 2005 O'Donnell, 2005

*Abbreviations: TS, tumor-suppressor gene; OGoncogene; N/A, not applicable

miRNAs and Cancer – A Summary

- miRNAs control cell cycle, cell differentiation and apoptosis by regulating oncogenes and tumor suppressor genes
- miRNAs are misexpressed in cancer and are therefore excellent diagnostic/prognostic markers in cancer
- Some miRNAs e.g. *mir-155, can cause cancer and oncogenic miRNAs may be therapeutic targets in cancer*
- Other miRNAs like *let-7, may prevent cancer and may be therapeutic molecules themselves.*
- MicroRNAs could augment current cancer therapies.

References

- Role of miRNAs in Cancer and Apoptosis
  Lynan-Lennon Biol Rev Camb Philos Soc. 2009 Feb;84(1):55-71
- Causes and consequences of microRNA dysregulation in cancer
  Croce Nat Rev Genet. 2009 Oct;10(10):704-14.
- miRNAs as oncogenes and tumor suppressors. Zhang Dev Biol. 2007 Feb 1;302(1):1-1
- Transcriptional regulatory networks in Saccharomyces cerevisiae. Lee Science. 2002 Oct 25;298(5594):799-804.
- RNA regulation: a new genetics? Mattick Nat Rev Genet. 2004 Apr;5(4):316-23.
- microRNA functions. **Bushati Annu Rev Cell Dev Biol. 2007;23:175-205.**
- Mechanisms of post-transcriptional regulation by microRNAs: are the answers in sight?
  Filiowicz Nat Rev Genet. 2008 Feb;9(2):102-14.
- Post-transcriptional gene silencing by siRNAs and miRNAs.
  Filipowicz Curr Opin Struct Biol. 2005 Jun;15(3):331-41.
- The microRNAs of Caenorhabditis elegans. Lim Genes Dev. 2003 Apr 15;17(8):991-1008.
- A three-dimensional view of the molecular machinery of RNA interference.
  Jinek Nature. 2009 Jan 22;457(7228):405-12.
- miRNAs and Cancer AAAI Science Webinars February 20 with George Calin, Brank Slack and Scott Hammond
- Short RNAs repress translation after initiation in mammalian cells. Petersen Mol Cell. 2006 Feb 17;21(4):533-42.
- Raising the estimate of functional human sequence. Pheasant Genome Res. 2007 Sep;17(9):1245-53.
- A developmental view of microRNA function. Zhao Trends Biochem Sci. 2007 Apr;32(4):189-97.
- c-Myc-regulated microRNAs modulate E2F1 expression O'
  Donnnell Nature. 2005 Jun 9;435(7043):839-43.