

Your Genes and Your Health

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miRNA Regulatory Networks

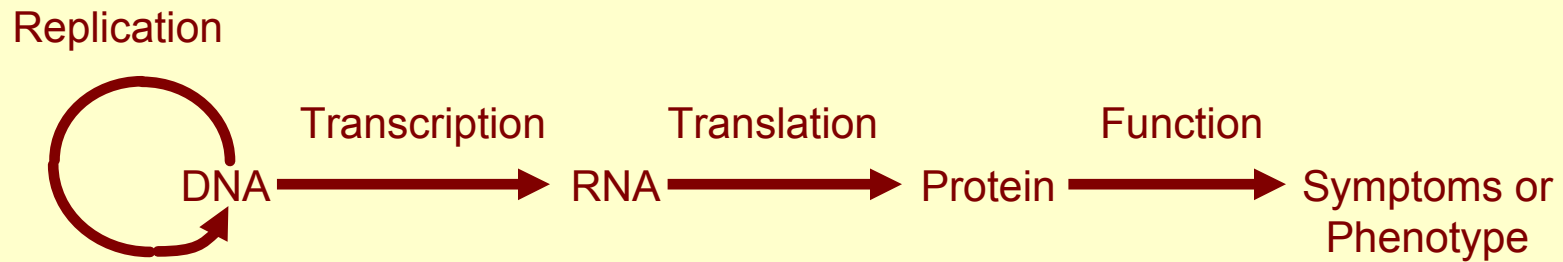


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Announcements

- 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

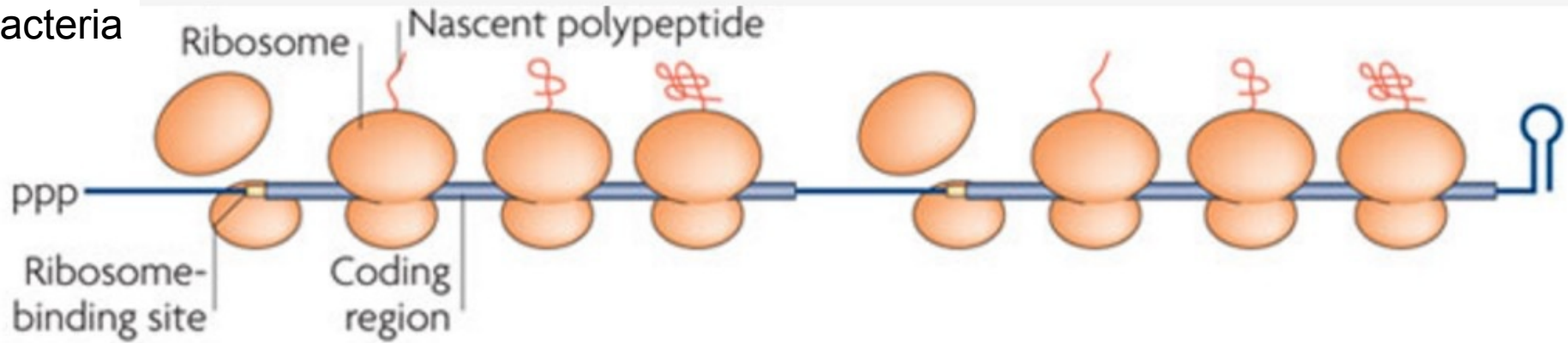


Gene Regulatory Mechanisms

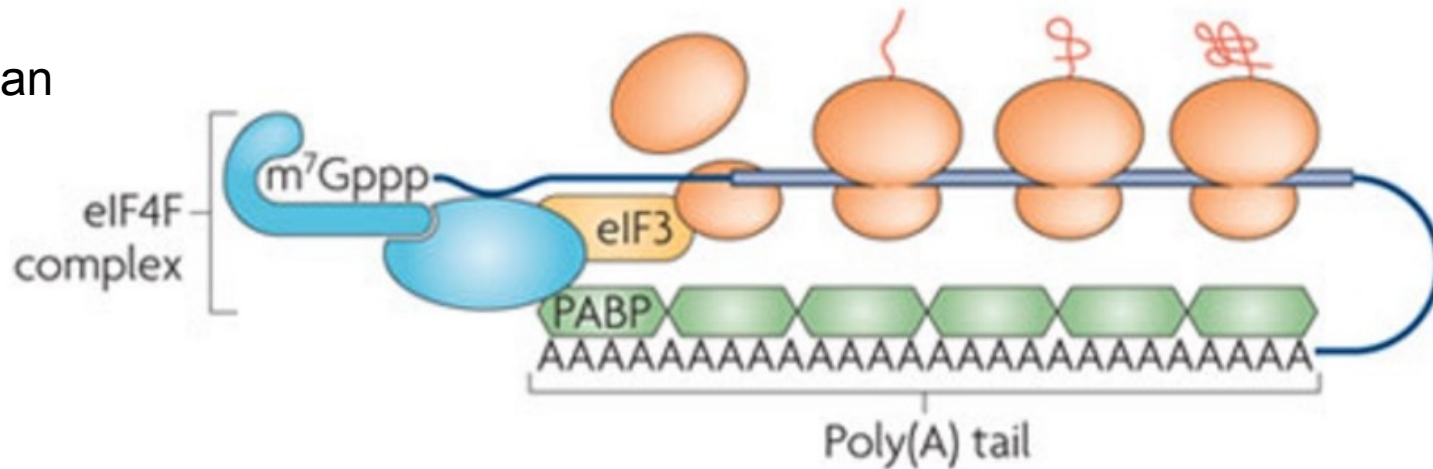
- Transcriptional Mechanisms
 - Type of promoters & RNA polymerase
 - Control of Transcription
 - Transcription Factors and TFBS
- RNA processing
 - Capping
 - Splicing and Alternative Splicing
 - Poly-Adenylation
- Translational Mechanisms
 - Micro RNAs (miRNAs) inhibit translation
 - Silencer RNAs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

Mechanism of Translation Mediated by Ribosomes

Bacteria



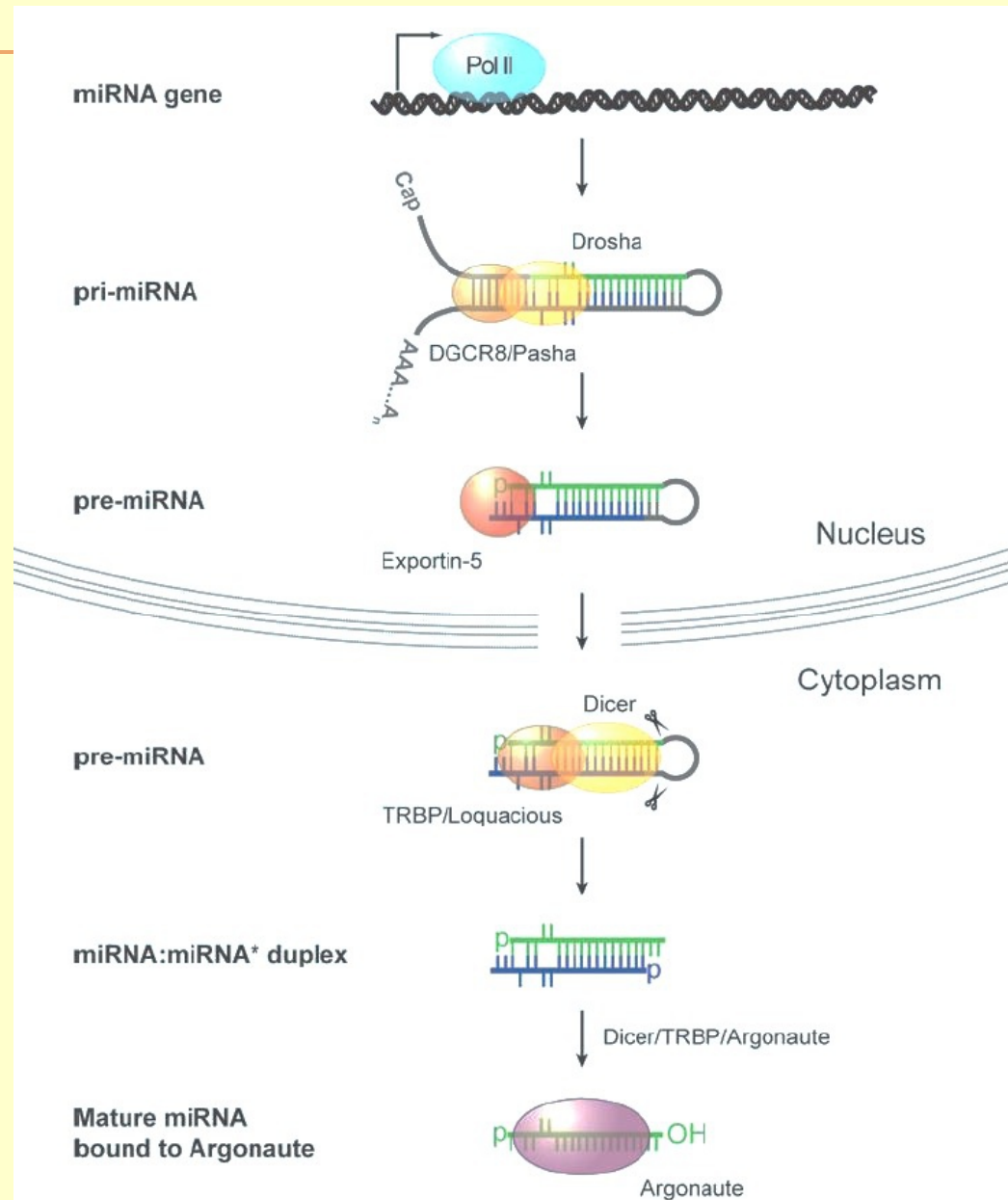
Human



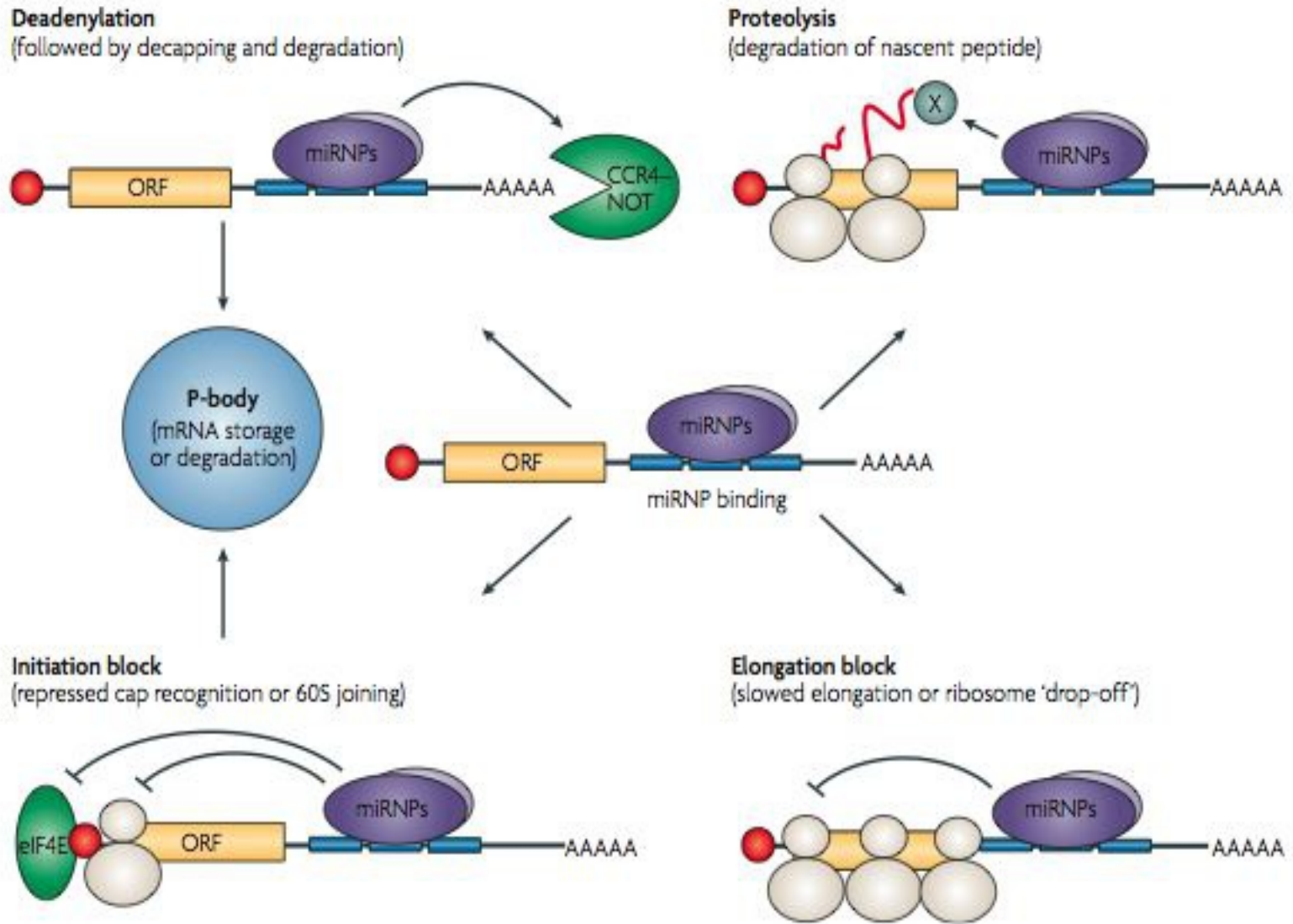
Regulation of Translation by microRNAs

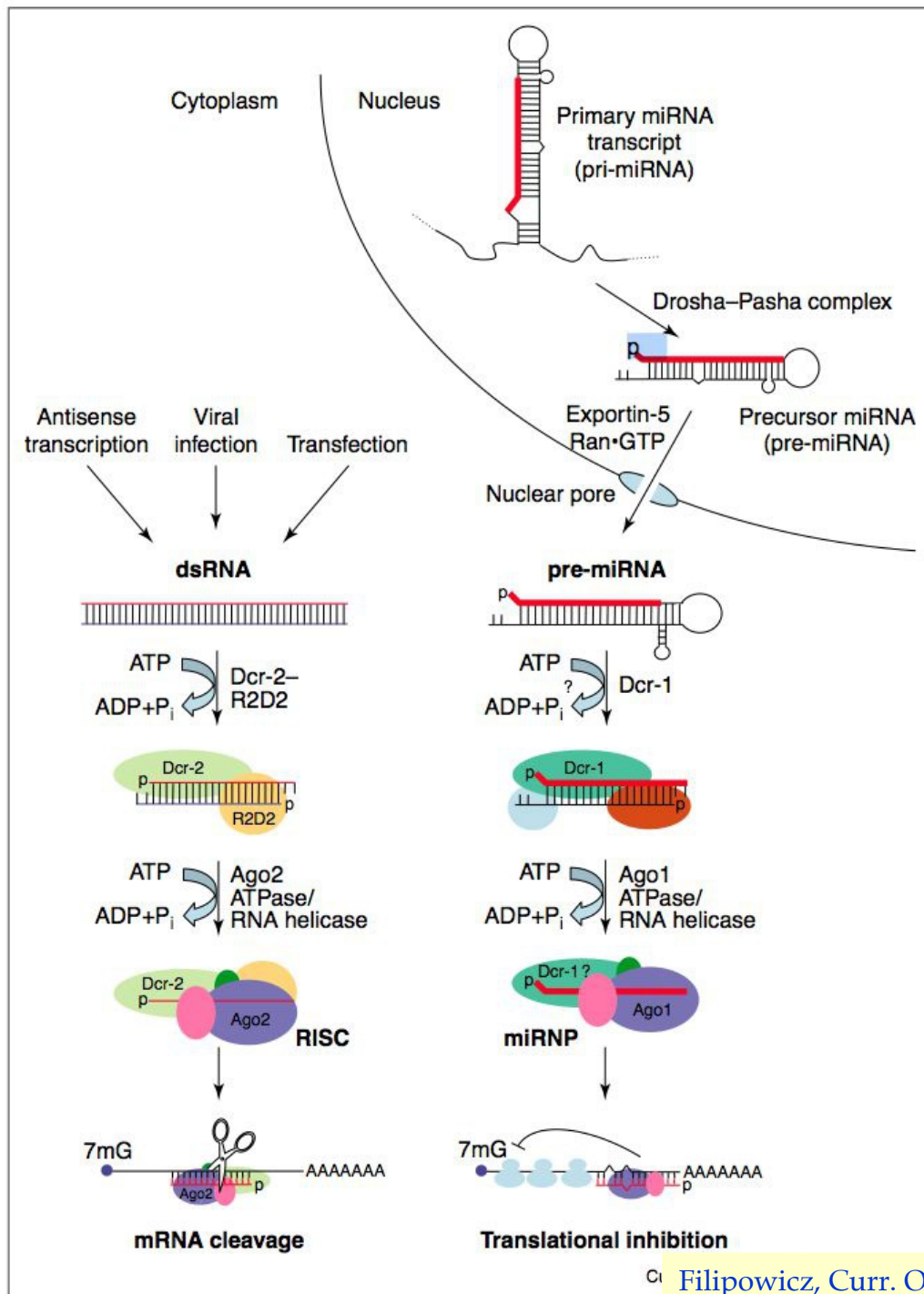
- MicroRNAs can inhibit translation of mRNAs and cause degradation of mRNAs
- Micro RNAs form an RNA-Induced Silencing Complex (RISC) that can both inhibit translation and degrade mRNA
- MicroRNA RISC complexes bind to the 3' UTR regions of mRNAs and stop translation and induce mRNA degradation

microRNA Biogenesis



Mechanisms of Translational Regulation by miRNP Complexes





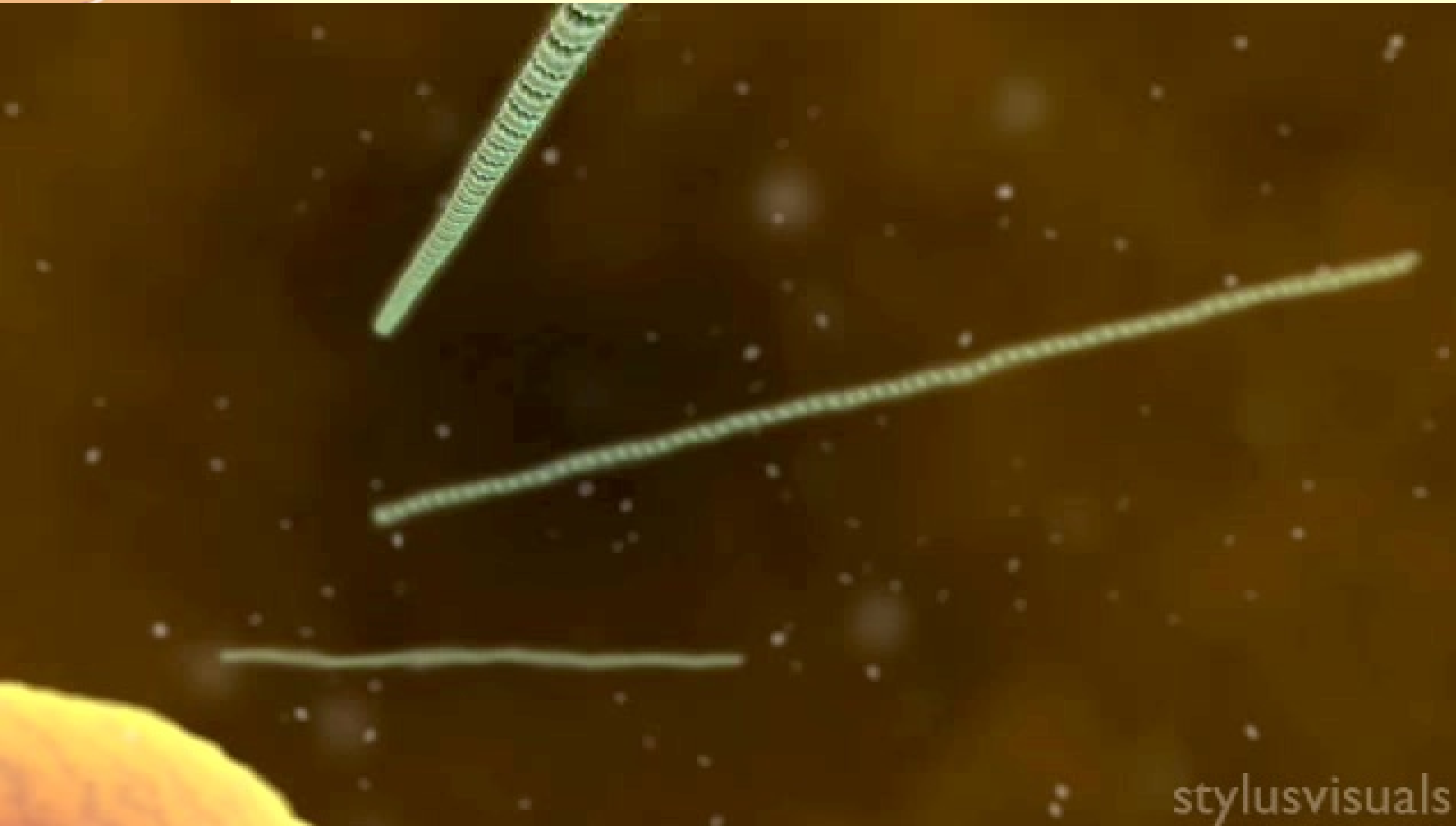
siRNA mediated degradation of mRNA

versus

miRNA mediated inhibition of mRNA translation

Dicer Mechanism

(New York Museum of Modern Art - MOMA)

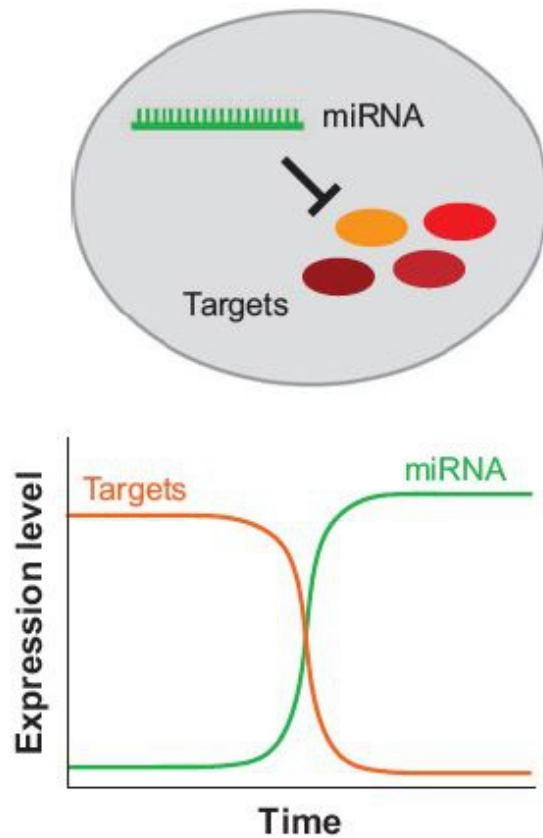


stylusvisuals

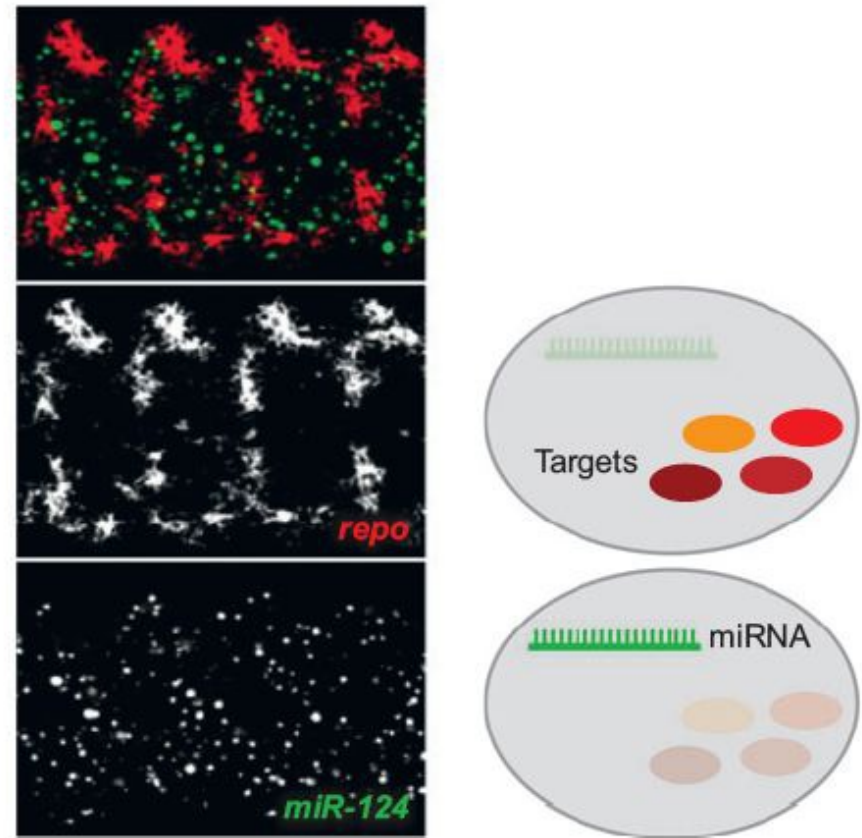


miRNA Expression Results in Temporal and Spatial Reciprocity with Target Expression

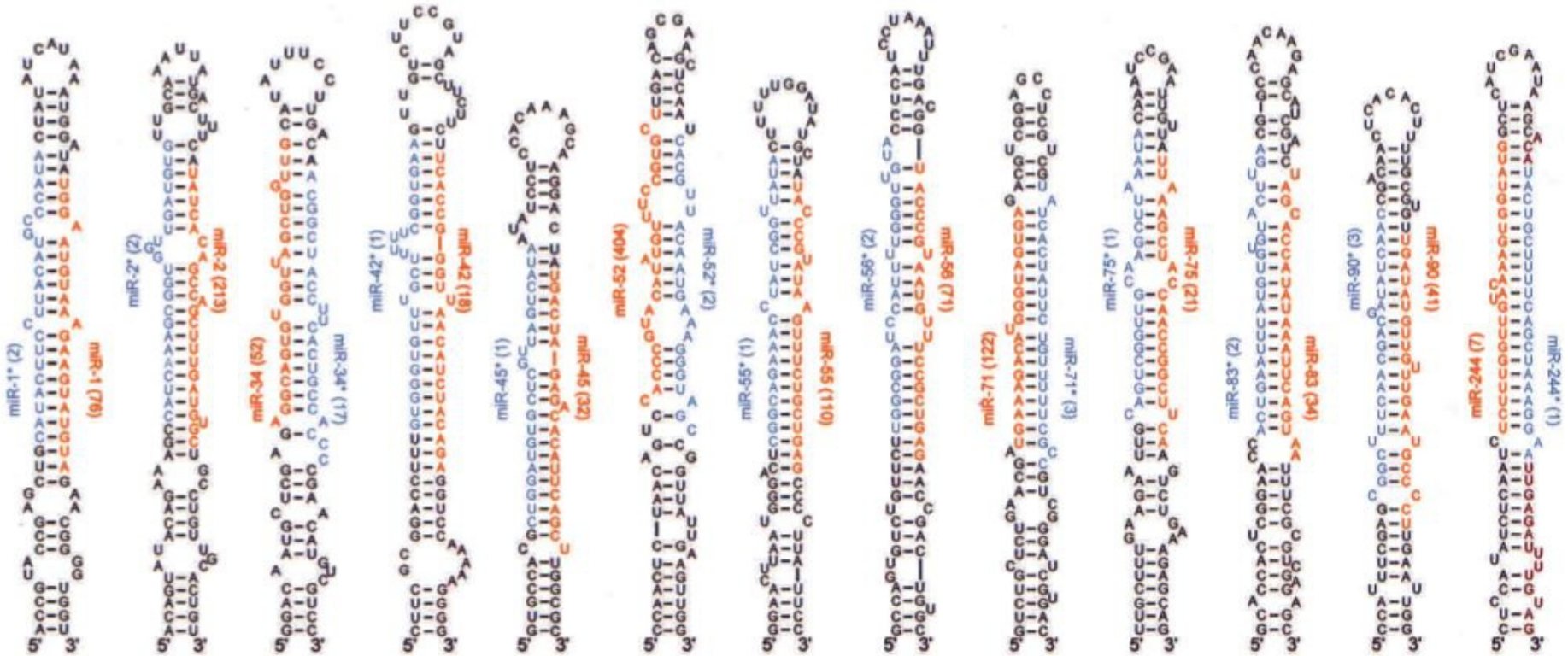
a Temporal reciprocity



b Spatial reciprocity



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)

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

lin-4 family

```
UCCUGAGA . . . CCUAACUUGUGA Hs miR-125b-1
UCCUGAGA . . . CCUAACUUGUGA Hs miR-125b-2
UCCUGAGA . . . CCUAACUUGUGA Ce lin-4
UCCUGAGA AUUCUGAACAGCUU Ce miR-237
```

let-7 family

```
AGAGGUAGUAGGUUGCAUAGU . . . Hs let-7d
UGAGGUAGUAGGUUGUUAUAGU . . . Hs let-7e
UGAGGUAGUAGGUUGUUAUAGU . . . Hs let-7a-1
UGAGGUAGUAGGUUGUUAUAGU . . . Hs let-7a-2
UGAGGUAGUAGGUUGUUAUAGU . . . Hs let-7a-3
UGAGGUAGUAGGUUGUUAUAGU . . . Hs let-7a-4
UGAGGUAGUAGGUUGUUAUAGU . . . Ce let-7
UGAGGUAGUAGGUUGUUAUAGU . . . Hs let-7f-1
UGAGGUAGUAGGUUGUUAUAGU . . . Hs let-7f-2
UGAGGUAGUAGGUUGUUAUAGU . . . Hs miR-98
UGAGGUAGUAGGUUGUUAUAGU . . . Hs let-7g
UGAGGUAGUAGGUUGUUAUAGU . . . Hs let-7i
UGAGGUAGUAGGUUGUUAUAGU . . . Hs let-7b
UGAGGUAGUAGGUUGUUAUAGU . . . Hs let-7c
UAGGUAGU . . . UUCAUUGUUGGG Hs miR-196-1
UAGGUAGU . . . UUCAUUGUUGGG Hs miR-196-2
UGAGGUAGUAGGUUGUUAUAGU . . . Ce miR-84
UGAGGUAGG . . . CUCAGUAGUUGCA Ce miR-48
UGAGGUAGG . . . UGC . . . AGAAAUUGA Ce miR-241
```

mir-1 family

```
UGGAAUGUAAAAGAAUGUA A Hs miR-1b
UGGAAUGUAAAAGAAUGUA U Hs miR-1d
UGGAAUGUAAAAGAAUGUA . . . Ce miR-1
UGGAAUGUAAAAGAAUGUA . . . Hs miR-206
```

mir-9 family

```
UCUUUGGUUAA . . . CUGCUG . . . UAUUA Hs miR-9-1
UCUUUGGUUAA . . . CUGCUG . . . UAUUA Hs miR-9-2
UCUUUGGUUAA . . . CUGCUG . . . UAUUA Ce miR-244
```

mir-10 family

```
AACCC . . . GUAGAUCGAAACU . . . UUGU . . . Hs miR-100-1
AACCC . . . GUAGAUCGAAACU . . . UUGU . . . Hs miR-100-2
CAACC . . . GUAGAUCGAAACU . . . UUGU . . . Hs miR-99b
UACCCUGUAGA . . . UCGAGCUGUGUGU Ce miR-57
UACCCUGUAGA . . . UCGAGCUGUGUGU Hs miR-10a
UACCCUGUAGA . . . UCGAGCUGUGUGU Hs miR-10b
AACCC . . . GUAGAUCGAAACU . . . UUGU . . . Hs miR-99a
UACCC . . . GUAGAUCGAAACU . . . UUGU . . . Ce miR-51
```

mir-19 family

```
UGUGCAAUUC . . . UAU . . . GCAAAACUGA . . . Hs miR-19a
UGUGCAAUUC . . . UAU . . . GCAAAACUGA . . . Hs miR-19b-1
UGUGCAAUUC . . . UAU . . . GCAAAACUGA . . . Hs miR-19b-2
. . . UGCAAUUC . . . UAU . . . GC . . . ACUGUAGG Ce miR-254
```

mir-25 family

```
UAUUUGCACUUGUC . . . CGGC . . . CUGU Hs miR-92-1
UAUUUGCACUUGUC . . . CGGC . . . CUGU Hs miR-92-2
UAUUUGCACUUGUC . . . CGGC . . . CUGU Ce miR-235
CAUUUGCACUUGUC . . . UGGU . . . UUGA Hs miR-25-1
CAUUUGCACUUGUC . . . UGGU . . . UUGA Hs miR-25-2
UAUUUGCACUUGUC . . . UGGU . . . UUGA Hs miR-32
```

mir-29 family

```
. . . UAGCACC AUUUUGAAAUCAGUGUU Hs miR-29b-1
. . . UAGCACC AUUUUGAAAUCAGUGUU Hs miR-29b-2
. . . UAGCACC AUUUUGAAAUCAGUGUU Hs miR-29b-3
. . . UAGCACC AUUUUGAAAUCAGUGUU Hs miR-29c
. . . UAGCACC AUUUUGAAAUCAGUGUU Hs miR-29a-1
. . . UAGCACC AUUUUGAAAUCAGUGUU Hs miR-29a-2
. . . UAGCACC AUUUUGAAAUCAGUGUU Ce miR-83
```

mir-31 family

```
AGGCAAGAUGUUGGCA . . . U . . . AGC . . . Ce miR-72
. . . GGC AAGAUGUUGGCA . . . U . . . AGCUG Hs miR-31
UGGCAAGAUGUUGGCA . . . U . . . AGC . . . Ce miR-73
```

mir-34 family

```
AGGCAGUGUGUUA . . . GCUGGUUG . . . Ce miR-34
UGGCAGUGUGUUA . . . GCUGGUUGU Hs miR-34
UGG . . . AGUCU . . . ACAAU . . . GGUUGUUGU Hs miR-122a
```

mir-50 family

```
UGAUUUGUAAUUC . . . AGCUUACAG . . . Ce miR-62
UGAUUUGUAAUUC . . . AGCUUACAGU Hs miR-50
UGAUUUGUAAUUC . . . AGCUUACAGU Hs miR-190
UGAUUUGUAAUUC . . . AGCUUACAGU Ce miR-90
```

mir-74 family

```
UGG . . . AGAGAA . . . AGGCAGUUC . . . Hs miR-185
UGGC . . . AGAAAU . . . AGGCAGU . . . CUACA Ce miR-74
```

mir-76 family

```
UCCGU . . . UGUUG . . . AU . . . GAAGCCUUGA Ce miR-76
UCCGU . . . UGUUG . . . AU . . . GAAGCCUUGA Hs miR-187
```

mir-79 family

```
A . . . AAAAGCUAGC . . . UACCAAAAGCU . . . Ce miR-79
. . . AAAAGCUAGC . . . UACCAAAAGCU . . . Hs miR-131
U . . . AAAAGCUAGC . . . UACCAAAAGCU . . . Ce miR-75
```

mir-80 family

```
UGAGAUCATC . . . GU . . . GAAAGCCUAGU Ce miR-81
UGAGAUCATC . . . GU . . . GAAAGCCUAGU Ce miR-82
UGAGAUCATC . . . GU . . . GAAAGCCUAGU Ce miR-80
UGAGAUCATC . . . GU . . . GAAAGCCUAGU Hs miR-143
```

mir-105 family

```
UCAAAUUC . . . UCA . . . GACUCCUUGU . . . Hs miR-105-1
UCAAAUUC . . . UCA . . . GACUCCUUGU . . . Hs miR-105-2
. . . UAAAUGCA . . . UGUUAACUGCUGUGA Ce miR-232
```

mir-124 family

```
U . . . AAGGCACGCG . . . GU . . . GAAUGCCA . . . Hs miR-124a
U . . . AAGGCACGCG . . . GU . . . GAAUGCCA . . . Hs miR-124a
U . . . AAGGCACGCG . . . GU . . . GAAUGCCA . . . Hs miR-124a
. . . U . . . AAGGCACGCG . . . GU . . . GAAUGCCA . . . Ce miR-124
. . . AAUGGCAC . . . UGCAU . . . GAAU . . . UCA . . . CGG Ce miR-228
. . . AAUGGCAC . . . UG . . . GUA . . . GAAU . . . UCA . . . CUG Hs miR-183
```

mir-133 family

```
. . . UUGGUCCCCU . . . UCAACCAGCUGU Hs miR-133a-1
. . . UUGGUCCCCU . . . UCAACCAGCUGU Hs miR-133a-2
. . . UUGGUCCCCU . . . UCAACCAGCUGU Hs miR-133b
A . . . UUGGUCCCCU . . . UCAACCAGCUGU Ce miR-245
```

mir-137 family

```
U . . . AAUUGCU . . . C . . . AGAAUACCCUU . . . Ce miR-234
. . . AAUUGCU . . . C . . . AGAAUACCCUU . . . Hs miR-137
```

mir-141 family

```
U . . . AAUACUGUC . . . AGGUAAU . . . GAC . . . CCU Ce miR-236
. . . AAUACUGUC . . . AGGUAAU . . . GAC . . . CCU Hs miR-141
```

mir-193 family

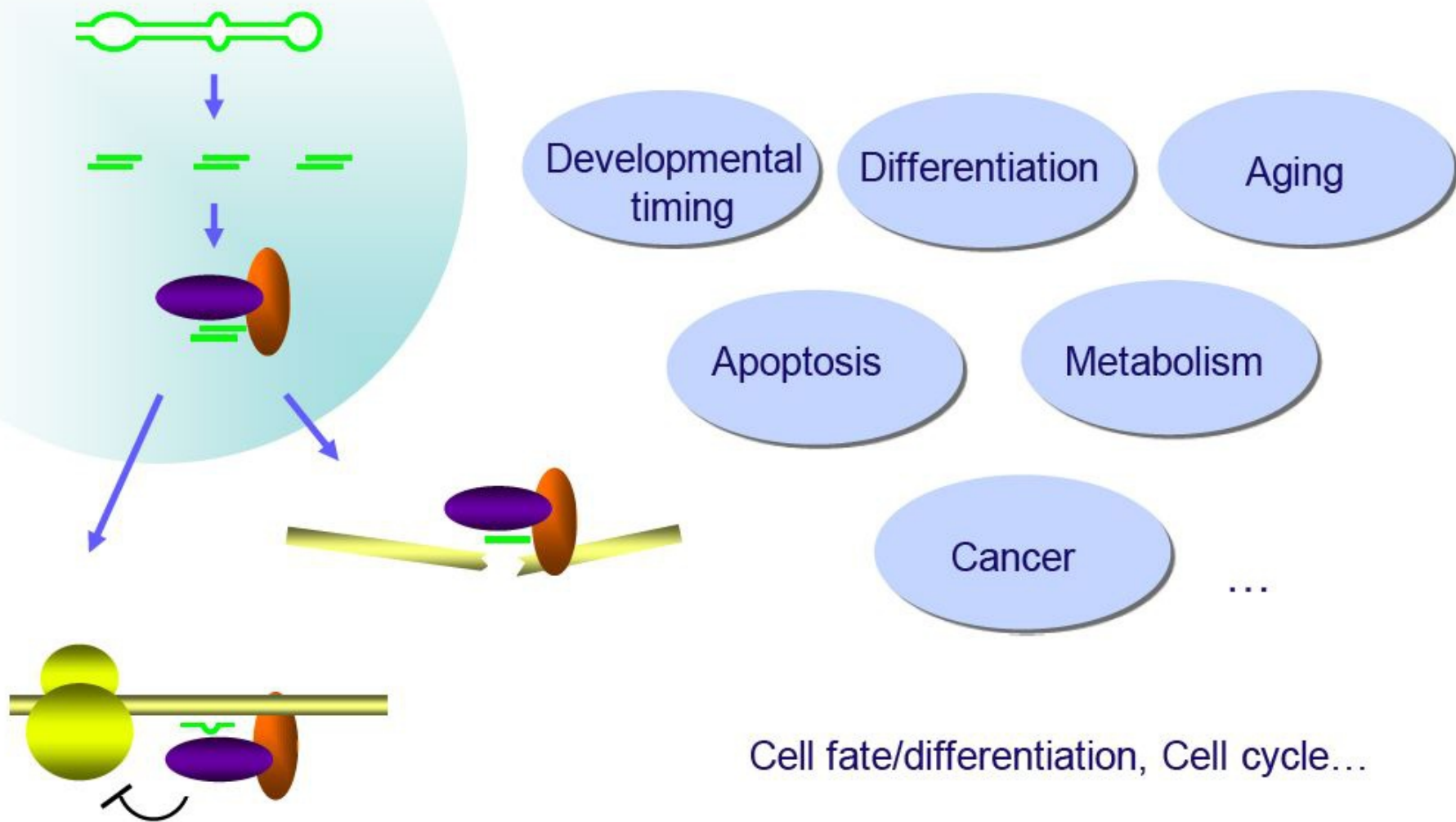
```
U . . . ACUGGCC . . . C . . . CAAA . . . UC . . . UUC . . . CCU Ce miR-240
A . . . ACUGGCC . . . C . . . CAAA . . . UC . . . UUC . . . CCU Hs miR-193
```

mir-220 family

```
C . . . CACACCC . . . UCA . . . CU . . . AACACUGAC Ce miR-253
C . . . CACACCC . . . UCA . . . CU . . . AACACUGAC Hs miR-220
```



Thousands of microRNAs act in multiple biological events



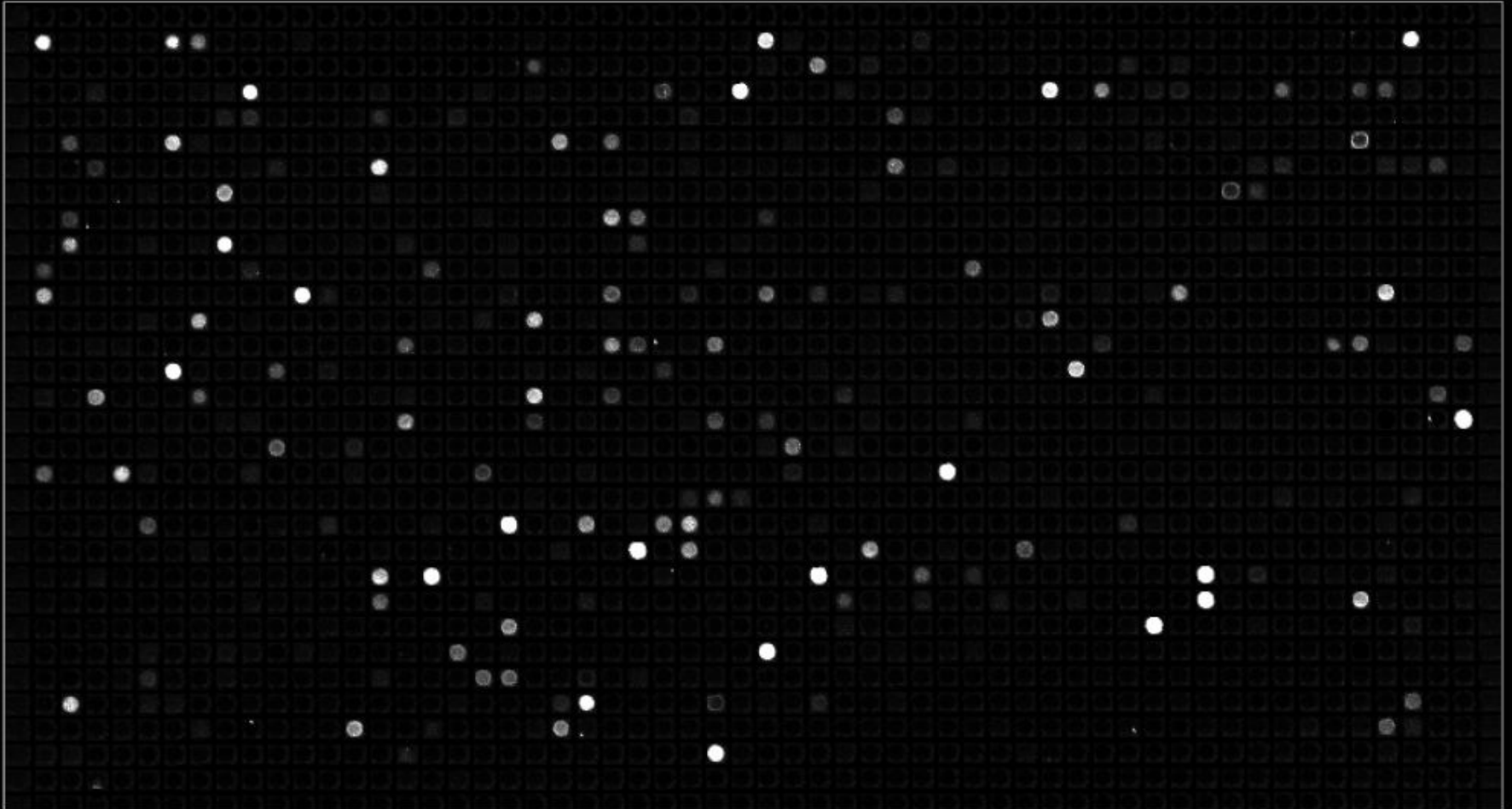
***ALTERATIONS OF MICRORNAS ARE FOUND IN EVERY
TYPE OF HUMAN CANCER***



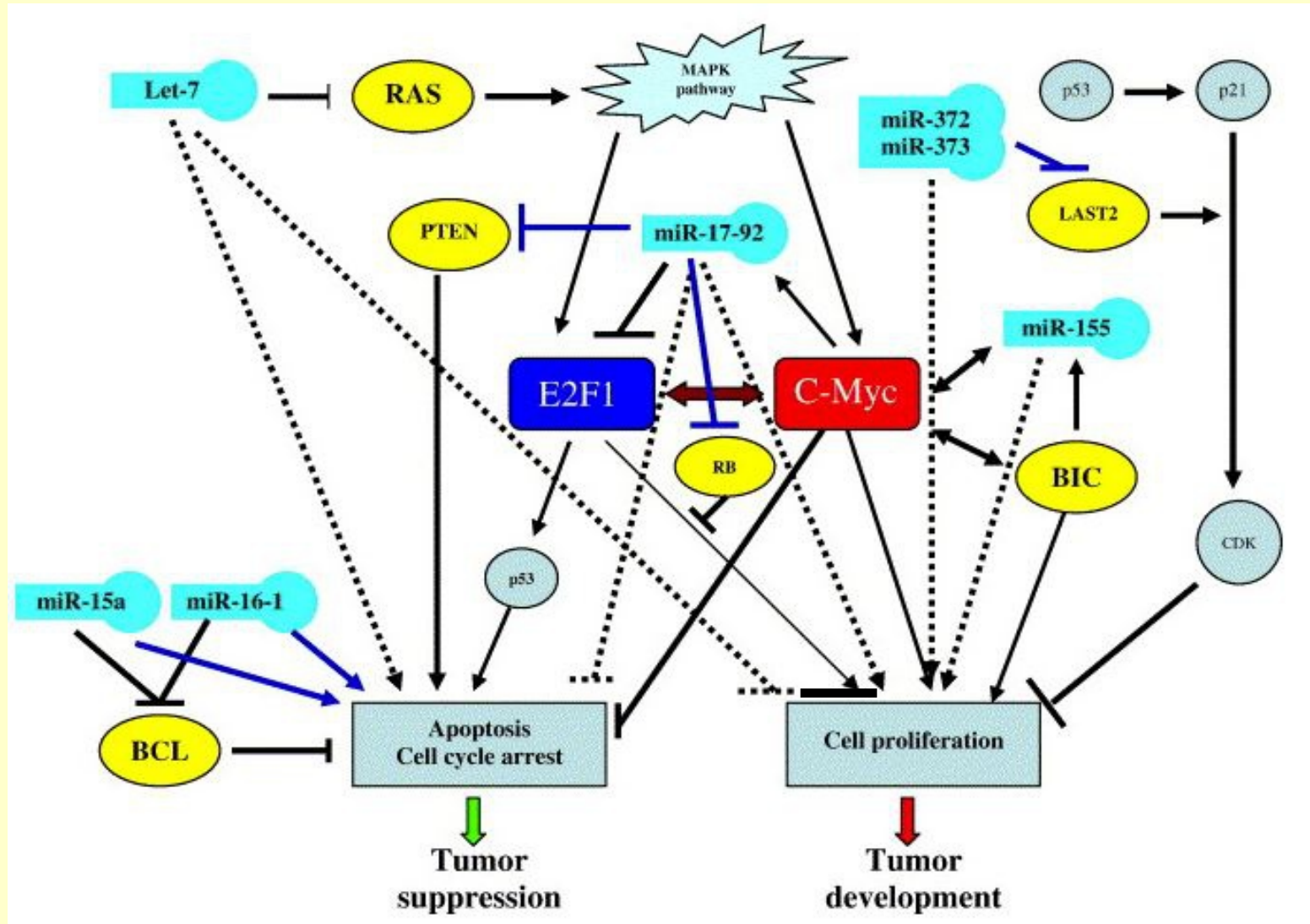
**miRNA
expression profiles
classify
human leukemias
and
carcinomas**

(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



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 cellines. 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
<i>let-7</i>	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 <i>mir-142</i> 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 cluster in hepatocellular carcinoma. Over-expressed in Bcell lymphomas.	TS/ OG	He, 2005 O'Donnell, 2005

*Abbreviations: TS, tumor-suppressor gene; OG oncogene; 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.

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