Strange and Unexpected Genetics

RNA interference

http://www.pbs.org/wgbh/nova/sciencenow/3210/02.html

http://www.hhmi.org/biointeractive/rna/rnai/index.html

Review Session:
Wed May 14 this room, 1-2 PM
YOU provide the questions
This is true, but....

**Activators**
The regulatory proteins bind to DNA at distant sites known as enhancers. When DNA folds so that the enhancer is brought into proximity with the transcription complex, the activator proteins interact with the complex to increase the rate of transcription.

**Repressors**
These regulatory proteins bind to "silencer sites" on the DNA preventing the binding of activator to nearby enhancers and so slowing transcription.

**Basal factors**
These transcription factors, in response to coactivators, position RNA polymerase at the start of a protein-coding sequence, and then release the polymerase to transcribe the mRNA.

**Coactivators**
These transcription factors transmit signals from activator proteins to the basal factors.
The Petunia Mystery

Co-Suppression: The transgene inhibits both the expression of the transgene AND the endogenous gene.
Make antisense RNA of your favorite gene

Inject

Mutant Phenotype

No translation????
Make sense RNA of your favorite gene

HOW?

Inject
Make sense RNA of your favorite gene

Make antisense RNA of your favorite gene

Gene

Transcription

Messenger RNA

Antisense RNA

Duplex formation

Double Stranded RNA

Inject

Mutant Phenotype

Caenorhabditis elegans

Pharynx

Gut

Gonad

Eggs

Vulva
RNA Interference is a Biological System that Recognizes dsRNA and Inactivates Corresponding mRNAs in a Sequence Specific Manner.

**ALARM!!**

- dsRNA
- Dicer
- 22 nt
- Small Inhibiting RNA (siRNAs)
- Assemble into RISC Complex
- Perfect Base-pairing to mRNA
- mRNA Cleavage and Destruction

Andrew Z. Fire
Craig C. Mello
2006 Nobel
A WHOLE NEW WAY OF GENE REGULATION

Why is it there?
A Protection against RNA viruses

Dicer
Activated RISC
Viral RNA breakdown
Less Virus
Regulation of “normal” gene function

1. miRNA gene expression

2. miRNA processing

3. miRNA-guided mRNA cleavage
The human genome contains about 250 miRNA genes, and perhaps most mRNAs could be a target.

Lots of people are trying to figure out all the relationships between miRNA expression and protein expression from other mRNAs. Major implications for cancer, development and stem cell biology.
Genome wide screens of gene function

Functional studies using RNAi

~19,000 C. elegans genes
>50% have human homologues

Degradation of target mRNA
Loss of function phenotype

C. elegans

Drosophila

Humans

E. coli

Long >150 bp dsRNA

>100 bp

Bathing

Transfection

Dicer, RISC loading

RISC loading
Inhibit your favorite mRNA from your favorite organism

1. miRNA gene expression

2. miRNA processing

3. miRNA-guided mRNA cleavage
Future?

Cancer treatment:
Break down the mRNA for the signal or telomerase

AIDS treatment:
Break down viral RNA

Cosmetic treatment:
Get blue eyes, lighter skin
Block fat production
The take-home message