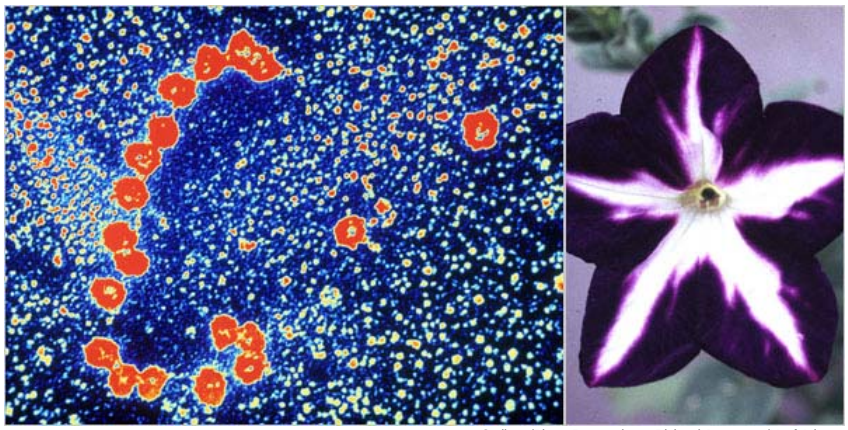
The Promise and Power of RNA



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RNA turns out to be far more important than previously thought. Left, messenger RNA, active in protein production; right, silencing RNA turns off the gene that makes the purple pigment in this petunia.

By ANDREW POLLACK
Published: November 10, 2008

People whose bodies make an unusually active form of a certain protein tend to have dangerously high levels of cholesterol. Those with an inactive form of the protein have low cholesterol and a low risk of heart attacks.

Needless to say, pharmaceutical companies would love to find a drug that can attach itself to the protein and block its activity. That might be difficult for this protein, which is called PCSK9.

But a powerful new approach, called RNA interference, may surmount that obstacle. Instead of mopping up a protein after it has been produced, as a conventional drug would do, RNA interference turns off the faucet, halting production of a protein by silencing the gene that contains its recipe.

In monkeys, a single injection of a drug to induce RNA interference against PCSK9 lowered levels of bad cholesterol by about 60 percent, an effect that lasted up to three weeks. Alnylam Pharmaceuticals, the biotechnology company that developed the drug, hopes to begin testing it in people next year.

The drug is a practical application of scientific discoveries that are showing that RNA, once considered a mere messenger boy for DNA, actually helps to run the show. The classic, protein-making genes are still there on the double helix, but RNA seems to play a powerful role in how genes function.

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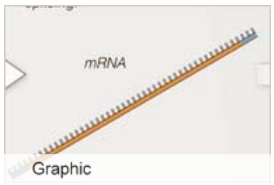

A Bestiary of RNA

David Corcoran, a science editor, explores some of the topics addressed in this week's Science Times.

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Thoughts on Genes (November 11, 2008)

"This is potentially the biggest change in our understanding of biology since the discovery of the double helix," said John S. Mattick, a professor of molecular biology at the University of Queensland in Australia.

And the practical impact may be enormous.

RNA interference, or RNAi, discovered only about 10 years ago, is attracting huge interest for its seeming ability to knock out disease-causing genes. There are already at least six RNAi drugs being tested in people, for illnesses including cancer and an eye disease.

And while there are still huge challenges to surmount, that number could easily double in the coming year.

"I've never found a gene that couldn't be down-regulated by RNAi," said Tod Woolf, president of RXi Pharmaceuticals, one of the many companies that have sprung up in the last few years to pursue RNA-based medicines.

The two scientists credited with discovering the basic mechanism of RNA interference won the Nobel Prize in Physiology or Medicine in 2006, only eight years after publishing their seminal paper. And three scientists credited with discovering the closely related micro-RNA in the 1990s won Lasker Awards for medical research this year.

RNA and DNA are strands made up of the chemical units that represent the letters of the genetic code. Each letter pairs with only one other letter, its complement. So two strands can bind to each other if their sequences are complementary.

Genes, which contain the recipes for proteins, are made of DNA. When a protein is to be made, the genetic code for that protein is transcribed from the DNA onto a single strand of RNA, called messenger RNA, which carries the recipe to the cell's protein-making machinery. Proteins then perform most functions of a cell, including activating other genes.

But scientists are now finding that a lot of DNA is transcribed into RNA without leading to protein production. Rather, the RNA itself appears to be playing a role in determining which genes are active and which proteins are produced.

Much attention has focused on micro-RNAs, which are short stretches of RNA, about 20 to 25 letters long. They interfere with messenger RNA, reducing protein production.

More than 400 micro-RNAs have been found in the human genome, and a single micro-RNA can regulate the activity of hundreds of genes, said David P. Bartel, a biologist at the Whitehead Institute in Cambridge, Mass., and at the Massachusetts Institute of Technology.

As a result, Dr. Bartel said, the activity of more than half the genes in the human genome is affected by micro-RNA.

"It's going to be very difficult to find a developmental process or a disease that isn't influenced by micro-RNAs," he said.

Indeed, scientists have found that some micro-RNAs contribute to the formation of cancer and others help block it.

Other studies have found micro-RNAs important for the proper formation and functioning of the heart and blood cells.

Scientists are also finding other types of RNA, some of which may work differently from micro-RNA. By now, there are so many types of RNA that one needs a scorecard to keep track.

Besides micro-RNA (miRNA), the new ones include small interfering RNA (siRNA), piwi-interacting RNAs (piRNA), chimeric RNA, and promoter-associated and termini-

associated long and short RNAs. They join an existing stable that included messenger RNA (mRNA), transfer RNA (tRNA), and small nucleolar RNA (snoRNA), which all play roles in protein production.

Scientists do not know what all the newly discovered RNA is doing. Some of it may be just a nonfunctional byproduct of other cellular processes.

And there is still uncertainty over how big a role RNA plays. Some scientists say proteins are like a light switch, turning genes on and off, while RNA usually does fine tuning, like a dimmer.

Still, the many new discoveries are "revealing a level of regulation and complexity that I don't think the current organizational model of the genome ever envisioned," said Thomas R. Gingeras, professor and head of functional genomics at Cold Spring Harbor Laboratory.

Despite the remaining mysteries, researchers and companies are moving rapidly to exploit the latest findings. While micro-RNAs are getting some attention, the biggest effort is on RNA interference.

RNA interference is induced when a short snippet of double-stranded RNA — called a small interfering RNA, or siRNA — enters a cell. The cell treats it much like a micro-RNA it might make on its own. That results in the silencing of a gene that corresponds to the inserted RNA.

Scientists believe that RNA interference evolved as a way to fight viruses, since double-stranded RNA is rare outside viruses.

Given that the sequences of genes are now known, it is fairly straightforward to synthesize a small interfering RNA that can serve as a drug to silence a gene. Still, there has not yet been a truly convincing demonstration that such drugs will work in people.

One risk is that the small RNA snippets might silence genes beyond the intended target. And that could mean that a drug based on these snippets would have unwanted side effects.

But the biggest challenge is getting the RNA into the cells where it is needed. Double-stranded RNA is rare outside viruses, so the cell is not likely to welcome it.

"Double-stranded RNA basically to the body means one thing: a virus," said Jonas Alsenas, a biotechnology analyst at the securities firm Leerink Swann who is skeptical about RNAi drugs.

Double-stranded RNA can set off an immune response. Enzymes in the blood tear RNA apart. And even if the RNA survives a trip through the bloodstream, it can have difficulty entering the target cells.

"Most of the cell membranes are negatively charged and the RNA is negatively charged, so they won't get close to each other," said Dr. Mohammad Azab, president of Intradigm, an RNA interference company.

Still, startups like Intradigm, Tekmira Pharmaceuticals, Calando Pharmaceuticals, MDRNA and Traversa Therapeutics are developing delivery methods.

Chemical changes can be made to RNA to make it more stable and to avoid setting off the immune system. And the RNA can be inserted into little globules of fat or attached to polymers to help it get through the bloodstream and enter cells.

RXi is developing an oral delivery method for treating certain immune diseases. In some cases, though, these packages can introduce their own toxicities.

Delivery problems tripped up an earlier gene-silencing technology called antisense, which uses single strands of RNA instead of double strands. But progress is now being made in antisense as well, so it may turn out that antisense drugs will compete with RNAi drugs.

Given the delivery challenges, the first RNAi drugs are for uses that do not require delivery through the bloodstream.

Alnylam is testing a drug that can be inhaled to treat a respiratory virus. Three other companies are testing drugs to treat age-related macular degeneration, the leading cause of blindness among the elderly. The drugs are injected directly into the eye.

The most advanced of the eye drugs, developed by the Miami-based Opko Health, is in the final stage of clinical trials, which would give it a shot at being the first RNAi drug to reach the market.

But some systemic delivery is now being tried. Quark Pharmaceuticals has started early human testing of a drug to prevent kidney damage. Since the kidney removes RNA from blood for excretion, much of the drug is expected to end up there anyway.

Similarly, lipids tend to end up in the liver. Since cholesterol is also processed in the liver, lipid particles will be used to deliver Alnylam's PCSK9 anticholesterol drug, as well as one it plans to test against liver cancer.

"If all we ever get to is the liver, we'll be having our hands full with human disease," said John Maraganore, chief executive of Alnylam. But he and other industry executives say they will eventually learn to deliver RNAi drugs anywhere in the body.

One shortcoming of RNA interference is that it can only turn genes off. But to treat some diseases, like those in which the body makes too little of a protein, it might be desirable to turn genes on or to increase their activity levels.

In one of the latest surprises in this field, scientists have found that RNA can do this too. They have discovered what they call RNA activation, or RNAa. The molecules that perform it are called either small activating RNAs (saRNA) or antigene RNAs (agRNA).

"We weren't looking for it," said David Corey, a professor of pharmacology at the University of Texas Southwestern Medical Center in Dallas, who was one of those to discover the phenomenon about two years ago.

Scientists in his lab were attempting to silence genes using RNAi directed at the promoters of genes. A promoter is a region of DNA that helps activate a gene.

Instead of being silenced, the genes became more active and protein production increased. Dr. Corey said it appeared that the RNA enhanced the activity of proteins that bind to the gene promoters.

Whether RNA activation can be used for therapy remains to be seen. It does show, however, that the limits of RNA activity have yet to be understood. There is more to come.

A version of this article appeared in print on November 11, 2008, on page D1 of the New York edition.

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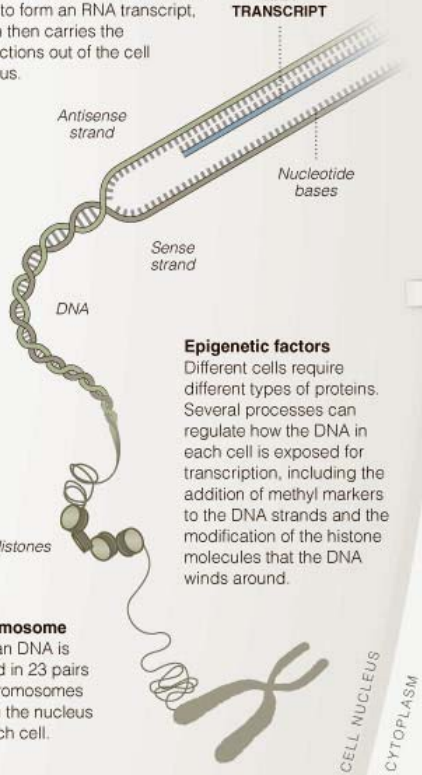
November 11, 2008

A Bestiary of RNA

Once thought to be simply a messenger between the DNA and the protein-building processes of a cell, RNA now seems to play a powerful role in how genes function. New types of drugs hope to make use of some of the many types of RNA to halt or reduce the production of specific proteins.

RNA transcription
Human DNA contains thousands of genetic recipes for proteins, which perform most functions of a cell. To build a protein, a section of DNA unwinds, exposing the nucleotide bases. The strand that contains the protein recipe is copied letter by letter to form an RNA transcript, which then carries the instructions out of the cell nucleus.



Epigenetic factors
Different cells require different types of proteins. Several processes can regulate how the DNA in each cell is exposed for transcription, including the addition of methyl markers to the DNA strands and the modification of the histone molecules that the DNA winds around.

Chromosome
Human DNA is stored in 23 pairs of chromosomes within the nucleus of each cell.

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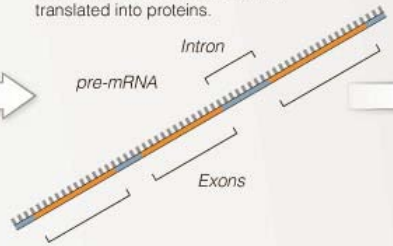
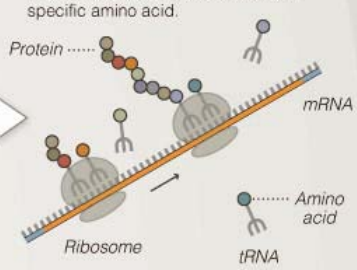
Precursor messenger RNA (pre-mRNA)
Some RNA transcripts are cut into segments. Noncoding parts of the transcript, called introns, are cut out and discarded, leaving behind exons, the parts of the transcript that will be translated into proteins.

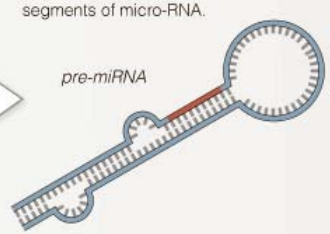


Messenger RNA (mRNA)
The exons are spliced together into a strand of messenger RNA, a recipe for a specific protein. Different combinations of the exons might form different protein recipes, a process called alternative splicing.

Protein translation
Ribosomes build proteins by matching sets of three base pairs on the messenger RNA with a single transfer RNA (tRNA), each of which carries a specific amino acid.

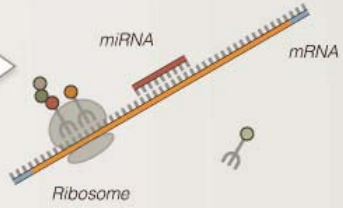


Precursor micro-RNA (pre-miRNA)
Other RNA transcripts are cut and folded by enzymes into hairpin shapes, which are then processed and sliced into short segments of micro-RNA.

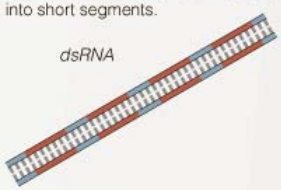


Micro-RNA (miRNA)
These short segments of RNA, each about 20 letters long, are thought to affect the activity of more than half the genes in the human genome.

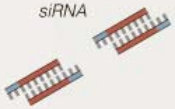
RNA interference: Blocking translation
If a micro-RNA binds to a matching region on a strand of messenger RNA, it will block the ribosome from reading the strand and disrupt protein production.



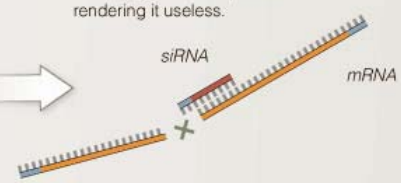
Double-stranded RNA (dsRNA)
Rare outside of viruses, long double strands of RNA are treated as hostile by the body. If a double strand does enter the cell, an enzyme will dice it into short segments.



Small interfering RNA (siRNA)
The resulting snippets of RNA are about 20 letters long. Drug companies are trying to artificially synthesize these snippets to match specific gene sequences.



RNA interference: Cutting mRNA
The small interfering RNA will bind to a segment of messenger RNA that matches its sequence, triggering the messenger RNA to split and rendering it useless.



Sources: Nature; Science

JONATHAN CORUM/THE NEW YORK TIMES

This chart has been revised to reflect the following correction:

Correction: November 12, 2008

A chart on Tuesday describing RNA transcription, with an article about the promise of research into RNA, reversed the label for the sense and antisense strand of DNA.