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Telling Jewels From Junk in DNA

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Our DNA holds about 20,000 protein-coding genes. To make a protein, a cell makes a copy of the corresponding gene, in the form of a single-stranded molecule called RNA. The cell uses the RNA molecule as a template to make the protein. And then the protein floats off to do its job.

Some of our genes don't encode proteins; instead, they create long RNA molecules that don't serve as protein templates. They have different jobs.

One of these so-called long-noncoding RNAs (lncRNAs, for short) is vital to women's health. Women carry two copies of the X chromosome, of course, while men have only one. Yet both sexes produce the same number of proteins from X chromosomes. The cause of that balance is a lncRNA called Xist.

In each cell in a woman's body, Xist locks onto one of the two X chromosomes and inactivates it. Then the cell is able to produce proteins only from the X chromosome free of Xist. If that bit of RNA fails, women produce extra proteins. Studies on mice suggest this can lead to cancer.

Xist is far from a fluke. In a study published last year, a team of researchers identified more than 58,000 different kinds of lncRNAs made by human cells. But it is not clear what they all do, or even if they do anything at all.

Some researchers argue that most lncRNAs don't serve any function and are probably just sloppy cellular accidents.

They point out that a lot of DNA in the human genome is little more than padding between genes. LncRNA doubters maintain that sometimes a cell's protein-making machinery accidentally reads a stretch of this socalled junk DNA and

spews out a useless RNA molecule. The cell promptly destroys the molecule, correcting its mistake.

Dr. Hoard Y. Chang is not one of them. In a study published last week in the journal Genes & Development, he and his colleagues were able to discover a number of functional lncRNAs. To do so, they used an innovative method to explore millions of years of RNA evolution.

One clue that a gene may have an important function is that it hasn't changed much in millions of years. Gene mutations tend to be harmful, and they are less likely to get passed down to future generations.

lncRNAs are long, flexible strands, with a few hooks they use to latch onto certain pieces of DNA.

Mutations that alter the long stretches of RNA between these hooks may not have much effect on how they work. Over millions of years, related lncRNA genes may pick up so many mutations that their evolutionary histories can be hidden.

Dr. Chang and his colleagues reasoned that lncRNA genes might still hold onto a little similarity over time and across related species: In order for lncRNAs to keep working, those hooks shouldn't change much.

To test their idea, the scientists investigated the history of one wellstudied lncRNA genecalled roX, discovered in the common fruit fly in 2008. If roX can't work, male flies die. Subsequent research revealed why.

RoX is the mirror image of Xist in humans. In male flies, roX grabs onto the male's single X chromosome and puts it into overdrive. "The amount of gene activity is cranked up twofold," said Dr. Chang. Thanks to roX, males make as many X chromosome proteins as females and thereby thrive.

Dr. Chang and his colleagues searched for roX-like genes in closely related species of flies. Instead of trying to find matches for the entire roX gene, they only looked for stretches that matched the hook-encoding parts of the gene.

They identify roX genes in 47 species. The fact that these flies share a common ancestor that lived 40 million years ago suggests that these newly identified genes have some impressive staying power and encode lncRNAs important to survival.

Dr. Chang's team also performed a transplant, replacing the roX gene in the common fruit fly with genes from other species. Fairly often, the transplanted gene was able to take over roX's job and keep male flies alive. This method may help scientists figure out whether other lncRNAs are sloppy accidents or essential molecules.

In their new report, Dr. Chang and his colleagues also describe an examination of a long-noncoding RNA molecule called HOTAIR, found in humans and mice.

Like roX and Xist, it has a crucial job to carry out. "It has an important role in telling cells their location in the body," Dr. Chang explained. Without HOTAIR, mice develop a host of birth defects in their skeletons.

In their new study, Dr. Chang and his colleagues discovered that HOTAIR is present not just in humans and mice, but in 43 species of vertebrates, a veritable menagerie including armadillos, alligators and zebrafish.

The common ancestor of all of these species lived 400 million years ago. It's possible that HOTAIR was telling cells their location in our aquatic ancestors even back then.

Those experimental tests remain to be carried out, said Dr. Chang, "but the new work suggests a road map for how to get to that knowledge."

Please answer the following two questions: (請作答在答題紙上)

1. What do Xist and roX do, respectively? (50%)
2. What are 2 obvious characters among Xist, roX, and HOTAIR? (50%)