

Rewriting the Textbooks

Even the smallest details of our genetic information have a story to tell. Meet two biologists who listened.

› Molecular biologist Christine Mayr is part of the Cancer Biology and Genetics Program at the Sloan Kettering Institute.

When Christine Mayr gives scientific presentations, she often starts with a picture of a worm—specifically, a millimeter-long soil dweller called *C. elegans*. This humble creature is a staple among biologists because it is one of the simplest organisms with a nervous system. It also has the virtue of being translucent, so you can see right through to its cells—all 959 of them.

C. elegans was the first multicellular organism to have its genome sequenced, in 1998. Researchers discovered at that time that it has about 20,000 genes. When the results of the Human Genome Project (the international effort to sequence our own genome) were unveiled just a few years later, researchers made a surprising discovery: Humans have the same number of genes as the worm.

For those of us who like to think we are more sophisticated, the discovery was a bit ego bruising. But it was also scientifically exhilarating. How to explain the vast difference in complexity between a worm and a human given this similar genetic endowment?

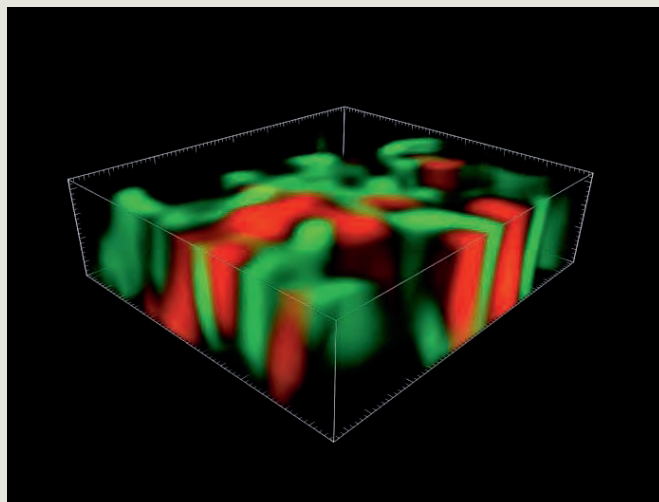
For Dr. Mayr, a molecular biologist in the Sloan Kettering Institute, that question led her to focus on a molecule that generally garners less of the limelight than DNA: RNA.

Like DNA, RNA is a nucleic acid made up of bases, represented by four letters, and carries genetic information. It serves as the messenger of that information, relaying it from the nucleus, where DNA is housed, to the cytoplasm, where proteins are made.

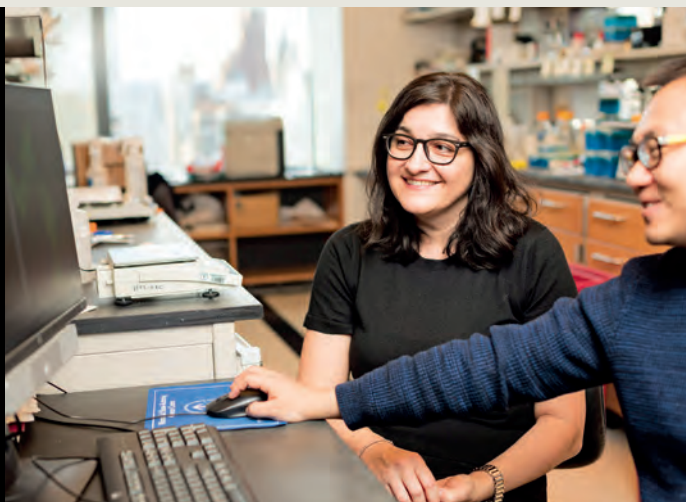
It might be easy to skip over the messenger, assuming it is ultimately less important than either DNA or protein. But Dr. Mayr thinks that messenger RNA (mRNA) has interesting stories to tell in its own right.

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Christine Mayr
MOLECULAR BIOLOGIST



▲ This three-dimensional reconstruction of the TIGER domain shows the close intermingling of the ER (green) with TIS granules (red). Read more about these structures on page 33.



▲ Dr. Mayr and postdoctoral fellow Weirui Ma (right) didn't set out to discover a previously unknown cell part. They were studying RNA-binding proteins.

Found: Missing Mutations

In a study published in *Nature* in August 2018, she and her colleagues found previously unknown cancer causes lurking in mRNA's message.

"If you sequenced just the DNA in cancer cells, you would not see these changes at all," Dr. Mayr says. "But these mRNA changes have the same ultimate effect as known cancer drivers in DNA, so we believe they may play a very important role."

The team looked specifically at chronic lymphocytic leukemia (CLL), a type of blood cancer. They chose this cancer in part because it's easier to obtain pure populations of cancer cells from a blood cancer than from a solid tumor. A colleague at MSK, physician-scientist Omar Abdel-Wahab, supplied blood samples from people with the condition — an exchange made possible by the close collaboration that exists between MSK's clinical and basic scientists. Using a method that Dr. Mayr's lab developed to detect these particular mRNA changes, the team found that a substantially greater number of people with CLL had an inactivation of a tumor-suppressor gene within the mRNA than those who had it in the DNA.

These findings help explain the long-standing conundrum that CLL cells have relatively few known DNA mutations. Some CLL cells lack any known mutations. In effect, the mRNA

changes that Dr. Mayr's team discovered could account for the missing DNA mutations.

A New Cell Part

Dr. Mayr has a knack for producing surprising discoveries. In November 2018, she and colleagues published an article in *Cell* announcing another radical finding that will have editors rewriting biology textbooks.

She and a postdoctoral fellow in the lab, Weirui Ma, discovered an entirely new cell part, known as an organelle. These small parts make up a cell's internal anatomy and perform specialized functions, like storing genetic information. The scientists dubbed their new organelle the TIGER domain.

This gel-like space occupies a large portion of the cell and is closely allied with the site where proteins are made. According to Dr. Mayr, the TIGER domain is where mRNA finds the appropriate environment in which to grow up.

"It's really a sorting mechanism," Dr. Mayr says. "The organelle admits specific mRNAs according to certain rules and excludes others. Then it shapes how the proteins made from those mRNAs will function."

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Weirui Ma

POSTDOCTORAL FELLOW





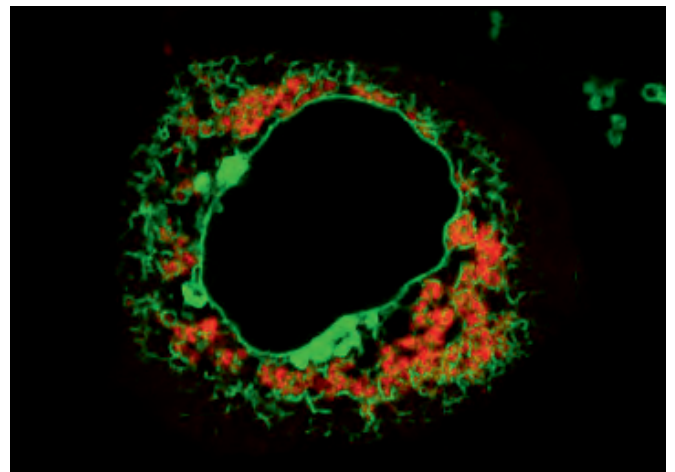
▲ In the lab, Drs. Mayr and Ma and others use imaging, biochemistry, and molecular biology techniques to conduct their research in human cells, mice, and budding yeast. They are studying how the untranslated regions of messenger RNAs regulate the function of proteins within cells.

The first three letters of TIGER stand for TIS granules; ER is for endoplasmic reticulum. (TIS granules are a network of interconnected proteins that bind RNA. ER is where new proteins are assembled.)

Dr. Ma named this space TIGER not only because the acronym fits but also because the striped pattern of the TIS granules interweaving with the ER resembles the orange-and-black coloring of a tiger. “We thought a lot about the name,” Dr. Ma says. “We wanted it to denote features of our finding and also be cool and easy to pronounce. One day I suddenly had a flash and ‘TIGER’ came to my mind.” Despite its fearsome-sounding name, the TIGER domain is actually a friendly place for protein interactions.

“Most people who study this topic think that if two proteins are present in the same area of a cell and bump into each other, that’s enough for them to interact,” Dr. Mayr says. “We’ve found that’s not the case. Some protein interactions can take place in the TIGER domain and nowhere else.”

The discovery of this domain was a delight to cell biologists and has opened their eyes to the possibility that other such hidden organelles are waiting to be discovered. ■



▲ This fluorescent microscopy image shows the distribution of the TIGER domain (red) in a cell. The black hole in the middle is the nucleus.