Research reveals link between tiny genetic structures and cancer

Perla Astudillo
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The complex connection between genes and cancer has been further clarified in fascinating findings published in the June 9 edition of the British science journal *Nature*. Separate studies by three major US cancer research laboratories have positively correlated the relationship between over 200 types of miRNA (also called microRNA) and the development of cancer tumours.

RNA, or Ribonucleic Acid, plays a crucial part in copying information contained in the genes on DNA strands in the cell nucleus and making it available in other parts of the cell involved in protein manufacture and other vital functions. MiRNA refers to small bits of RNA that break off larger pieces inside the cell nucleus. Its function has, until relatively recently, been poorly understood.

The latest research shows that miRNA is intimately involved in the regulation of all types of genes. Alongside the mapping of the human genome in 2003, it is one of the most significant findings in genetics in the past decade. The recent *Nature* articles provide new insights into how miRNA regulates genes, including those connected to various cancers.

MiRNA was discovered in 1993 by Harvard University scientist Rosalind C. Lee while investigating the genome of the soil worm *Caenorhabditis elegans*. Lee found that a specific microRNA, called lin-4, directly interfered with the level of protein produced during the worm's embryonic development. Essentially, it retarded the worm's development in its larval stages. It is now understood that the short strands of RNA perform a vital role in the cell by turning genes "on" or "off".

Over the past four years, more and more research has taken place into these tiny structures. In 2001, researchers published just four papers on the subject. In 2004, scientific journals contained nearly 200 papers featuring miRNA. The research has revealed that miRNA exists in plants and animals and affects such diverse functions as cell growth, death and fat metabolism in flies, as well as control of leaf and flower development in plants. Now miRNA has been directly linked to tumour formation.

Commenting on the latest *Nature* articles, James Carrington, Gene Research and Biotechnology director at Oregon State University, said: "For a long time, people did not know that these microRNAs were even there. In molecular biology, microRNAs are clearly one of the top two or three discoveries of the past decade." The point is further underscored by the *Nature* magazine web site, which reports that the microRNA findings remain number one on their "top ten" of downloaded articles—two months after publication.

All four *Nature* papers show that cancer formation can in some way be linked to miRNA. RNA has several functions inside the cell. "Messenger RNA," also known as "coding RNA", carries information from the nucleus for the manufacture of specific proteins. "Non-coding RNA" does not directly provide the data for specific proteins, but it does assist in their production. The various types of miRNA are part of the latter group of non-coding RNA structures.

The basic building blocks for RNA are known as nucleotides. MiRNA is just 21 to 25 nucleotides long, as compared to 80 million nucleotides in a basic chromosome inside the cell nucleus. Researchers have found more than 200 types of miRNA, but there could be up to 1,000 not yet discovered. Drawing an analogy with cosmology, Gary Ruvkun, a Harvard University researcher, has described miRNA as "the biological equivalent of dark matter—all around us but almost escaping detection".

Scientists have confirmed that 217 human miRNAs are directly involved in basic cellular processes. As Tony Golub MD, senior author of one of the *Nature* papers, explained: "The study opened our eyes to how much more there is to learn about genomic approaches to cancer." Golub, the Charles A. Dana Investigator in Human

Cancer Genetics at Dana-Farber Institute, commented: "[That] MicroRNA profiles have such potential diagnostic utility was a big surprise to us, and one we're keen to validate in future studies."

One of the *Nature* papers entitled "MicroRNA expression profiles classify human cancers" demonstrated that miRNA has the clear potential for aiding in cancer diagnosis. Researchers measured and profiled 217 miRNAs using an ingenious bead-based method to distinguish between the different samples—a difficult procedure because the miRNAs are so tiny. Each individual bead was marked with fluorescence "tags" so as to tell which specific miRNA was bound to it. It was also possible to determine how much of the miRNA was in a specific sample.

Researchers found that particular tumours were associated with certain types of miRNA. For instance, the miRNA involved in the development of leukaemia could be distinguished from miRNA that causes other cancers. In other words, it may be possible in the future to use miRNA profiling to determine if people have a predisposition to certain types of cancer.

In a second paper, a group of scientists at Cold Spring Harbor Laboratory in New York explained they were able to identify a cluster of microRNAs related to human lymphomas—cancers that derive from the body's immune cells.

Mice that were injected with a virus containing a certain miRNA cluster were more like to develop leukaemia than a control group that was not. The frequency of cancer went from about 30 percent for the control group to 100 percent for mice injected with the cluster. The presence of the miRNA cluster caused the tumours to arise much faster. The cancers were much more aggressive and killed the mice faster.

The ability for scientists to detect minuscule cellular structures is largely due to the huge developments in technology and in particular the processes of miniaturisation. For example, the biotechnology company US Genomics has produced a machine that can view miRNA molecules one at a time.

Called the Trilogy 2020 Single Molecule Analyser, it is one of many developments that are revolutionising genetics and molecular biology. In the past, scientists used what is known as the polymerase chain reaction (PCR) to reproduce large numbers of a particular genetic structure for testing or analysis. Now miRNA can be examined individually. A company spokesman explained: "If you need to see a needle in a haystack, you make a billion needles. That's what PCR does. We're able to see a single needle."

In late July, scientists at the University of Florida revealed miRNA is connected to certain birth defects, such as malformed limbs. By genetically modifying mice, scientists were able to observe for the first time how limbs develop in animals without the help of miRNAs. When miRNAs were not available to turn "off" certain genes, the mice grew malformed, nonfunctional limbs.

Commenting on the findings, Xin Sun, assistant professor of genetics at the University of Wisconsin, explained: "Many of the birth defects we see in people are mimicked by the defects we've seen in this mouse model. It indicates mutations in microRNAs might be responsible for birth defects, and this has not been discovered before." It also means that miRNA is involved in many more processes related to embryonic growth and development that previously considered by scientists.

Exactly how miRNAs contribute to diseases like cancer remains unclear, but the latest research has opened up new questions for scientists to tackle. In a letter in *Nature* accompanying the miRNA findings, Paul S. Meltzer commented: "Questions remain, of course. What regulates the expression of miRNAs? What are the targets of each miRNA?... We need to find out which of the biological pathways underlying cancer are regulated by miRNAs."

There is no doubt, however, that the latest findings have provided an important insight into the complex relationship between genetic structures and the processes of human development, including the onset of degenerative diseases such as cancer. While the research is still in its early stages, it holds out the possibility of developing the means for the early detection of cancers and new medical techniques for their prevention or treatment.