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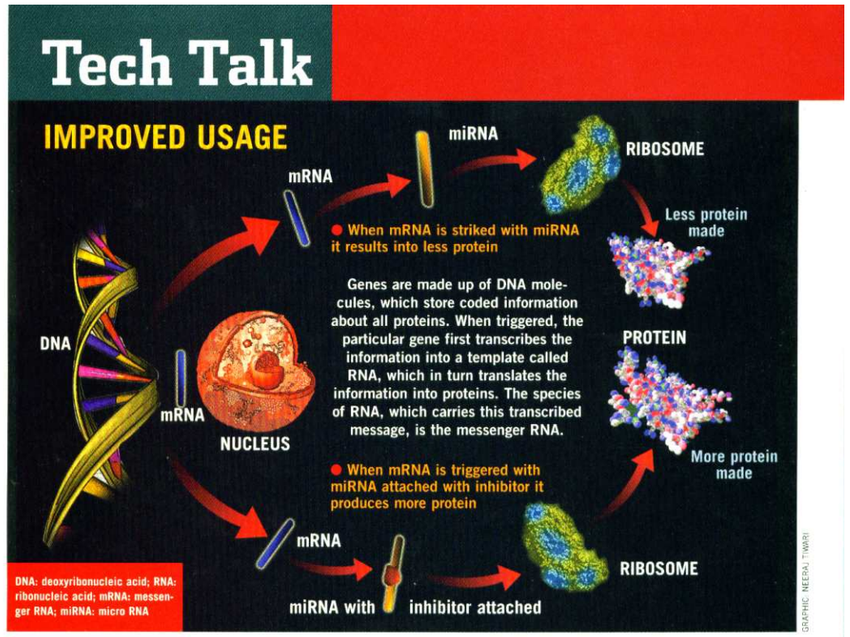

GENETICS

Fruitful Interference

by Noemie Bisserbe

New findings encourage scientists to use RNA in treatment of diseases

FOR DECADES, THE 'OTHER' GENETIC MATERIAL, RNA (ribonucleic acid), was thought to play only a supporting role to its more famous counterpart, DNA (deoxyribonucleic acid). After all, it is only used as an intermediary by the cells that produce protein. DNA-based genetic information first converts to transient RNA molecules, which are used by cells as blueprints to build proteins. But more recently, scientists have come to realise that the range of RNA functions is much broader. RNA can regulate or block some genes and mediate many key chemical reactions. These findings are leading scientists to use RNA in treatment of diseases such as AIDS and cancer.

Even though it has been supplanted in the course of evolution by DNA and proteins in many of its roles, RNA performs some core functions in cells ranging from bacteria to humans. "For example, two very large RNA molecules comprise the active site of the ribosome, the complex machine responsible for synthesising the proteins that catalyse most of the metabolic reactions essential for life," writes Jo Ann Wise, professor at the US-based National Science Foundation, division of molecular and cellular biosciences, in an email response to *BW*.

But the path-breaking discovery about the importance of RNA came about two years ago when scientists discovered a new class of RNAs: micro RNA (miRNA), Short Interfering RNA (siRNA). "These discoveries confirmed that RNA holds great potential in terms of its ability to control critical factors involving cell growth, metabolism and defence mechanism, and can be harnessed for therapeutic applications," says K.V. Subramaniam, president of Mumbai-based Reliance Life Sciences.

Adds Beena Pillai, scientist and researcher with the Delhi-based Institute of Genomics and Integrative Biology, "Scientists have for many years suspected that RNA might have had a

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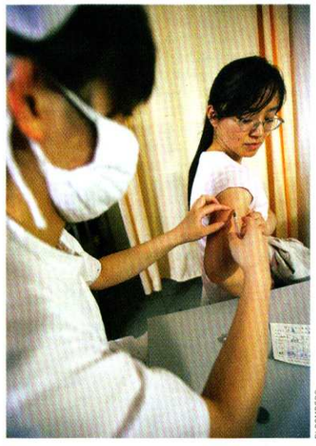
primitive role as the hereditary material. A few examples of RNAs carrying out enzymatic reaction are also known. But what has taken us by surprise is the sheer numbers and types of these molecules in the cell and, more importantly, the fact that they can regulate other genes." To put it simply, scientists found that RNA could block a gene from delivering its message to proteins, essentially shutting down that gene — a process called RNA interference.

Since then, scientists around the world have run with the idea, finding ways for RNA to turn off a variety of genes — in particular, those that cause disease. "The RNA interference pathway, through which tiny RNAs regulate gene expression at many stages through their ability to base pair with other nucleic acids, is a major focus of current excitement," says Wise. Several of these newly discovered small RNAs could crack code to hitherto unsolved medical mysteries. "Our own group has discovered small RNAs encoded by the human genome that can bind to HIV-1 genes and interfere with the replication of the virus in cultured human cells. We are now working on expanding this study to understand the value of this RNA as a marker for disease progression and as a therapeutic," says Pillai. Several groups now have found RNAs that are promising bio-markers for cancers — in other words they can be used in spotting cancer cells. "These may help in early diagnosis of the cancer type," she adds.


BLOOMBERG

RNA could soon have a role to play in prevention as well. Earlier this month, biomedical engineers at the University of Texas in Austin said they had developed a novel delivery system that could lead to more efficient and more disease-specific vaccines against infectious diseases. The findings use specific RNA molecules to significantly bolster a vaccine's effectiveness while tailoring it according to the type of immune response most desirable for a particular disease. "What we've achieved is a delivery system that provides DNA-based vaccines along with RNA, which allows us to significantly enhance the immune response and drive them into a certain direction that is effective against the disease," says Krishnendu Roy, associate professor, biomedical engineering and lead investigator on the study. The team's delivery system would work for a wide range of infectious diseases, making it a broad platform for infectious disease vaccines.

SHOWING POTENTIAL: Researchers claim new discoveries in RNA could lead to development of more disease-specific vaccines

Strong Results

In their studies using mice, biomedics at the University of Texas found immune responses were 5-50 times stronger in RNA-based vaccines compared to traditional ones. The stronger the immune response to a vaccine, the better protection the vaccinated person should have. The team worked with 'silencing RNA', which shuts down specific proteins in the body. "By silencing certain proteins in the cells that process your vaccine, we can direct the immune response one way or the other," adds Roy.

It may, however, still take some time before this vaccine is commercialised. Studies on mice will continue for the next four to five years. If the tests continue to prove successful, testing could begin on primates and, eventually, humans within six to ten years.

There have been other RNA-based discoveries as well, some revealing alarming facts. Researchers at Connecticut-based Yale University identified certain types of gene products in normal cells called chimeric RNAs and proteins thought to be found only in cancerous cells. These findings may bring new insights into how cancers operate and indicate that caution should be exercised in using chimeric gene products as markers for cancer, as is widely done now in cancer diagnosis. Also the discovery could mean that cancer drugs such as Novartis' Gleevec (known as Glivec in India) that target chimeric gene products may be more toxic than scientists earlier believed, as they also target normal cells.

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