New type of gene that regulates tumor suppressor PTEN identified

February 24 2013

Small stretches of DNA in the human genome are known as "pseudogenes" because, while their sequences are nearly identical to those of various genes, they have long been thought to be non-coding "junk" DNA.

But now, a new study led by scientists at The Scripps Research Institute (TSRI) shows how pseudogenes can regulate the activity of a cancer-related gene called PTEN. The study also shows that pseudogenes can be targeted to control PTEN's activity.

Published in the latest issue of the journal *Nature Structural & Molecular Biology*, the team's findings suggest a much larger role for pseudogenes than previously thought—a discovery that changes our understanding of the internal landscape of living cells, adding a new layer of complexity to an already crowded topography marked by multiple, overlapping, interacting gene networks.

Understanding how pseudogenes interact and control gene networks in the human body may lead to new ways of addressing diseases tied to problems that arise due to disruptions in these gene networks, said TSRI scientist Kevin Morris, PhD, who led the research in collaboration with scientists at the Karolinska Institute in Stockholm, Sweden, and The University of New South Wales in Sydney, Australia.

"This has improved our knowledge of how genes in cancer are regulated and how we may now be able to control them," Morris said.

Genes and Pseudogenes at Work

The focus of the human genome project, which decoded our entire DNA sequence a decade ago, was largely on genes—the genetic sequences that encode proteins and thus control processes that govern and regulate all biological functions. But these genes are only a small part of the genome. The vast majority of DNA in the human genome is non-coding, meaning that it does not make protein.

In the early days of molecular biology, scientists called these vast stretches of DNA "junk" because of their presumed inactivity. Pseudogenes, which make up vast swaths of non-coding DNA, were considered part of the junk—even though they resembled genes—because they did not code for proteins.

The results from the new study contradict that view by showing these bits of genetic material playing a profound role in controlling the activity of human genes. The control or loss of control of genes can make the difference between healthy and diseased tissue. In cancer, for instance, some genes become more active, while other genes that should normally shut down a cancerous growth become suppressed.

In the new work, Morris and his colleagues showed that pseudogenes can influence the activity of a human gene known as the phosphatase and tensin homolog (PTEN). PTEN has long been implicated in cancer and is categorized as a "tumor suppressor" gene, meaning that it has the ability to arrest the growth of a tumor. But in many forms of cancer, PTEN is shut down, allowing the tumor to grow unchecked.

Intriguing Possibilities

Morris and his colleagues found that pseudogenes sharing sequences in

common with PTEN can regulate the gene in two ways—knocking it down by suppressing the "promoter" for the PTEN gene, preventing the gene from being expressed, or soaking up PTEN-targeted regulatory micro-RNAs affecting the PTEN protein after the gene transcripts have been expressed.

Some companies are already looking at pseudogenes such as PTEN as targets of potential new drugs, Morris said, and the new work is a proof of principle that targeting pseudogenes can modulate the growth of cancer cells grown in the laboratory.

The same principle may be applicable to other diseases where the aberrant activity of a normal human gene is in play—or in infectious diseases, as a way of shutting down certain crucial genes belonging to viruses or bacteria.

Morris noted, however, there are many practical issues with controlling pseudogenes. Designing a drug targeting pseudogenes directly would be difficult to administer with current technology, as these drugs would need to be delivered into the exact cells where they are needed without spreading to other, healthy tissues where they could be toxic.

More information: 'A pseudogene long noncoding RNA network regulates PTEN transcription and translation in human cells', Per Johnsson, Amanda Ackley, Linda Vidarsdottir, Weng-Onn Lui, Martin Corcoran, Dan Grandér och Kevin V. Morris, *Nature Structural and Molecular Biology*, AOP 24 February 2013, doi: 10.1038/nsmb.2516

Provided by Karolinska Institutet