NATURE | SCIENTIFIC AMERICAN

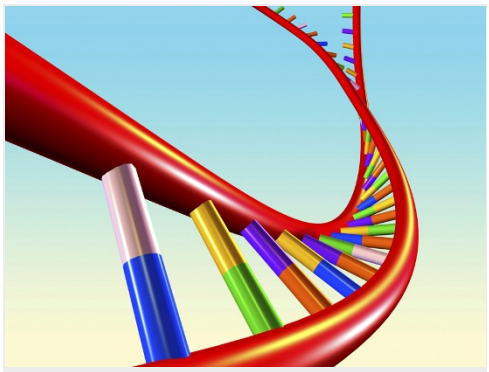
RNA fragments may yield rapid, accurate cancer diagnosis

A new method to noninvasively diagnose cancer and monitor its progression could eliminate the need for painful and sometimes life-threatening biopsies.

William Ferguson

31 January 2013

An article by Scientific American.



Purestock/Thinkstock

Strands of genetic information preserved inside microvesicles, called exosomes, may help scientists diagnose certain forms of cancer and monitor tumor progression.

Fragments of RNA that cells eject in fatty droplets may point the way to a new era of cancer diagnosis, potentially eliminating the need for invasive tests in certain cases.

Cancer tumor cells shed microvesicles containing proteins and RNA fragments, called exosomes, into cerebral spinal fluid, blood, and urine. Within these exosomes is genetic information that can be analyzed to determine the cancer's molecular composition and state of progression. Researchers at Massachusetts General Hospital discovered that exosomes preserve the genetic information of their parent cells in 2008, however exosomes have not seen widespread clinical testing as a means of cancer diagnosis until now.

"We have never really been able to detect the genetic components of a tumor by blood or spinal fluid," says Harvard University neurologist Fred Hochberg. "This is really a new strategy." He says exosome diagnostic tests could potentially detect and monitor the progression of a wide variety of cancers. He is one of the lead researchers in a multicenter clinical study using new exosomal diagnostic tests developed by New York City-based Exosome Diagnostics to identify a genetic mutation found exclusively in glioma, the most common form of brain cancer.

When treating other forms of cancer, surgeons are able to biopsy tumors to diagnose and monitor the state of the disease. For brain cancers like glioma, however, multiple biopsies can be life threatening. Bob Carter, head of neurosurgery at the University of California, San Diego, says well-preserved RNA in blood and spinal fluid enables researchers to test and monitor for these genetic changes noninvasively.

He says study researchers separate exosomes from bio-fluids with a diagnostic kit and then extract the relevant genomic information. Once the specific cancer mutation is identified, clinicians will periodically draw additional bio-fluids to monitor the mutation levels to determine whether a patient is responding to therapy.

Whereas Magnetic Resonance Imaging (MRI) is a useful tool, tumors only show up on imaging scans once they are at least one millimeter in diameter and comprise about 100,000 tumor cells. By that time, it may be too late for an early intervention. On the flip side, MRIs can also yield false positives. Hochberg says individuals who have been treated with conventional radiation therapy often have benign residual tissue from dying tumor cells that have been killed by the treatment but which the body has not yet eliminated. This tissue is often mistaken for tumor growth on a MRI scan. "You would identify to the patient that the drug is not working when in reality it is doing well," Hochberg says. "On the other hand, having an easily accessible biomarker for glioma would give you a clear response."

There are 18 U.S. hospitals participating in the clinical trial, sponsored by the Accelerated Brain Cancer Cure Foundation. Hochberg says study researchers have recruited 41 of 120 patients so far. Preliminary results will be presented in April at the International Society for Extracellular Vesicles Symposium in Boston.

From a technical standpoint I don't believe there is a barrier," Carter says. "This test can certainly be used now, what we are trying to finalize is the sensitivity and specificity of the test."

Exosomes may be a reliable method of screening for prostate cancer as well. A PSA test is currently the most common, noninvasive means to screen for prostate cancer in the U.S. PSA testing measures for elevated levels of prostate-specific antigen, a protein

produced by the prostate gland that is used to liquefy semen in men. The higher a man's PSA level, the more likely it is that he has prostate cancer, says James McKiernan, director of urologic oncology at Columbia University Medical Center. There are additional reasons, however, for high PSA levels-and some men with prostate cancer do not always have elevated PSA, he added. In addition, for many cases of prostate cancer, new research published in May 2012 in The New England Journal of Medicine shows that treatment does not actually extend the life of the patient.

"Honestly PSA is not cancer-specific," says Sudhir Srivastava, head of the National Cancer Institute's Cancer Biomarkers Research Group. "Exosomes could be very much [more] cancer specific. PSA might give you one specific biomarker for cancer identification, but exosomes can give you an entire disease specific profile so you would know whether or not it is a form of prostate cancer that necessitates treatment."

Researchers at Exosome have developed a diagnostic kit for prostate cancer with a diagnostic accuracy of around 75 percent-a rate comparable with that of actually taking a tissue biopsy, says Wayne Comper, a renal physiologist and chief science officer at Exosome. He says the first diagnostic kit could be available commercially by the end of 2013.

Researchers use the kit to look for the genetic biomarker TMPRSS2:ERG or T:E in exosomes taken from a urine sample. Comper says levels of T:E are nine times higher in a cancerous prostate versus a healthy one.

McKiernan says researchers found these exosomal diagnostic tests gave better predictive results for cancer than current prescreening methods, such as PSA. PSA levels are measured via a blood draw but also require a visit to a doctor's office for a digital rectal exam, something that isn't necessary with an exosomal diagnostic test. "Our study got enough interest to put together a series of sites for investigation to lead to potential FDA approval of this particular kit," he says. "That is ongoing right now and the last time I checked there were about 1,000 patients who have been enrolled in the study."

SCIENTIFIC AMERICAN™
More from *Scientific American*.

Srivastava says Exosome's prostate kit could prove to be extremely relevant in cancer treatment if it survives the U.S. Food and Drug Administration's grueling approval process. He says it is a precursor to what he hopes will be a series of multiple-gene-signature cancer tests. "We are looking for something with about 90 percent accuracy before it can be used by itself for clinical diagnosis," he says. "NCI has done two prostate trials with exosomes to date and is looking into creating standard isolation procedures to make the tests more specific."

In the meantime Srivastava says exosomal tests could be used in conjunction with current methods of diagnosis like PSA to help physicians better determine if the nature of a prostate tumor is severe enough to warrant radical treatment or removal without ever performing a biopsy. "If someone has high PSA and also has biomarkers which are positive in exosomes that would be a great test," he says. "Exosomes have the potential to really further the detection of cancer and help analyze things that would have otherwise not been detected noninvasively."

Nature | doi:10.1038/nature.2013.12344