UC San Diego Health

Ovarian Cancer-Specific Markers Set the Stage for Early Diagnosis, Personalized Treatments

Custom bioinformatics algorithm identifies human mRNAs that distinguish ovarian cancer cells from normal cells and provide new therapeutic targets

May 25, 2015 | Heather Buschman, PhD

Ovarian cancer is notoriously difficult to diagnose and treat, making it an especially fatal disease. Researchers at University of California, San Diego School of Medicine and Moores Cancer Center have now identified six mRNA isoforms (bits of genetic material) produced by ovarian cancer cells but not normal cells, opening up the possibility that they could be used to diagnose early-stage ovarian cancer. What's more, several of the mRNA isoforms code for unique proteins that could be targeted with new therapeutics. The study is published the week of May 25 by the *Proceedings of the National Academy of Sciences*.

"We were inspired by many studies aimed at using DNA to detect cancer," said first author Christian Barrett, PhD, bioinformatics expert and project scientist in the UC San Diego School of Medicine Institute for Genomic Medicine. "But we wondered if we could instead develop an ovarian cancer detection test based on tumor-specific mRNA that has disseminated from cancer cells to the cervix and can be collected during a routine Pap test."

While DNA carries all the instructions necessary for life, its actual sequence contains much more than just the genes that code for proteins. In contrast, mRNAs are complementary copies of just the genes. They carry the recipe for every protein that the cell will produce from the nucleus to the cytoplasm, where cellular machinery can read the recipe and build the corresponding proteins. According to the authors of this study, the advantage of using cancer mRNA for diagnosis rather than DNA is sheer number — a cancer cell might harbor just one or a few copies of a DNA mutation, but mRNA variants can occur in hundreds to thousands of copies per cell.

To determine if mRNAs can be used to distinguish ovarian cancer cells from normal cells, the team developed a custom bioinformatics algorithm and used it to mine two large public databases of genetic information — The Cancer Genome Atlas (TCGA) and the Genotype-Tissue Expression (GTEx) program, both sponsored by the National Institutes of Health. TCGA is a catalog of RNA and DNA from 500 tumors covering many cancer types, while GTEx is a database of RNA and

DNA from normal tissue samples. From these, the researchers were able to analyze mRNA sequence data from 296 ovarian cancers and 1,839 normal tissue samples.

Using this bioinformatics approach, the researchers identified six mRNA isoform molecules that have the tumor specificity required for an early detection diagnostic of ovarian cancer. They also validated their digital results in the real world using RT-quantitative PCR, a gene amplifying technique, to detect the same ovarian cancer-specific mRNA molecules in lab-grown cells.

Beyond their diagnostic potential, some of the mRNA isoforms identified in this study could also act as new therapeutic targets. These mRNA isoforms are predicted to encode proteins with unique amino acid sequences, which might allow them to be specifically targeted with certain therapeutics, such as monoclonal antibodies or T-cell-based vaccines. What's more, the ovarian cancer-specific mRNA isoforms themselves could also be targeted with new therapeutic drugs.

"Our experimental findings were made in a laboratory and were performed on ovarian cancer cells from cell lines," said study co-author Cheryl Saenz, MD, a clinical professor of reproductive medicine who specializes in treating gynecologic cancers. "Clinical trials will need to be conducted on women to confirm the presence of these markers in women that we know have cancer, as well as to document the absence of the markers in women that do not have ovarian cancer."

The authors acknowledge a few limitations to their approach, including technical limitations in detecting mRNA isoforms, a shortage of normal ovarian and fallopian tube control samples and the possibility that tumor cells that disseminate to the cervix may not genetically act the same as the primary tumor.

Still, based on these promising initial results, the authors recommend expanding their process for identifying tumor-specific mRNA isoforms to the 30 additional tumor types for which sufficient amounts of RNA sequence already exist.

Iris and Matthew Strauss, San Diego-based philanthropists who helped fund the study, are also excited by the promise this finding holds. "We created the Iris and Matthew Strauss Center for Early Detection of Ovarian Cancer in memory of our daughter, Stefanie Dawn Strauss," said Iris Lynn Strauss. "To further honor our daughter, we provided support for this study in an effort to help other women obtain early detection from this dreadful and deadly disease."

Additional co-authors of this study include Christopher DeBoever, Kristen Jepsen, Dennis A. Carson, and Kelly A. Frazer, all of UC San Diego.

This research was also funded, in part, by the National Cancer Institute (grant P30CA023100) and Colleen's Dream Foundation.

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Media Contact

Heather Buschman, PhD
858-249-0456
hbuschman@health.ucsd.edu

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