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Profiles in Cancer Research

Dr. David Sidransky

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Photo courtesy of Keith Weller

A longstanding and cruel fact of oncology is that the earliest stages of cancer are both the easiest to treat and the most difficult to detect. Most types of cancer have few symptoms in their early stages, and they have often spread throughout the body by the time of diagnosis.

Dr. David Sidransky has focused his career on looking for new and better ways to detect cancer early, before symptoms develop. His family encouraged him to be a doctor, and at Baylor College of Medicine he became fascinated with basic science while working with Dr. C. Thomas Caskey, a medical geneticist. He went on to train with Dr. Bert Vogelstein at Johns Hopkins University, a researcher "who was instrumental in my understanding of what I wanted to do in genetics and translational cancer research," he said.

Dr. Sidransky stayed on at Johns Hopkins to establish his own laboratory. In the early 1990s, in collaboration with Dr. Vogelstein, he published the first two studies (of bladder [2] and colorectal [3] cancer) showing that DNA shed from tumor cells could be measured in body fluids such as urine and stool. "When we found that we could detect these clonal genetic changes in bodily fluids, I think it was kind of a game-changer for everybody in the field," said Dr. Sidransky.

Much of the search for cancer biomarkers then and has now focused on measuring proteins produced by cancer cells. But few if any proteins are produced solely by cancer cells, and the same proteins produced at lower levels by normal tissues can complicate protein-based early cancer detection. In contrast, changes to DNA can be extremely specific for indicating the presence of cancer in the body.

The Sidransky laboratory is exploring the possibility of using DNA methylation, a type of epigenetic change that can contribute to cancer development, as a new type of biomarker for detecting early cancer. In a recent paper [4] they identified cancer-specific DNA methylation in 28 out of 53 genes that they tested. Eight of these genes showed cancer-specific DNA methylation in 300 tumor samples representing 13 different types of cancer.

"We believe that some of these methylation changes exist only in tumors; they're specific for the transformation process, and so they at least theoretically allow for more specific detection

of cancers at an early stage," said Dr. Sidransky.

These new biomarkers are being discovered at a time when they could have immediate clinical applications, explained Dr. Sidransky. As recently as a few years ago, detecting some types of cancer early would not have been useful because practical treatments were not available. For example, precancerous changes in the oral cavity (preneoplastic disease) often develops over a large area of the oral cavity at once. Surgery cannot be used in this case, and traditional chemotherapeutic drugs are so toxic that the risk-to-benefit ratio does not balance in favor of early treatment.

However, many newer biological agents such as some monoclonal antibodies and small-molecule inhibitors have a better safety record than traditional chemotherapy, making it feasible to use them for the prevention of disease progression. Dr. Sidransky's group is now testing the monoclonal antibody cetuximab [5] (Erbitux) in a clinical trial for patients with severe preneoplastic disease of the oral cavity.

"We wouldn't have thought of giving a traditional chemotherapeutic agent for even advanced preneoplastic disease," said Dr. Sidransky. "But the toxicities of the antibody are minimal and the survival advantage for patients is high, so we decided to try identifying the lesions that are likely to respond and giving those patients the drug now."

His laboratory is also exploring areas of research that may have both diagnostic and therapeutic applications in the future. For example, they have recently focused [6] on identifying changes in mitochondrial DNA that help drive cancer progression.

Dr. Sidransky enjoys mentoring young scientists who study in his laboratory because of the new and fresh perspectives that they often bring to research questions, but also because of what he believes will happen with the results of their hard work.

"I tell young investigators that this is an incredibly exciting time in cancer research. I think that in the next 5 years the entire human genome and epigenome is going to be mapped out in most major cancer types," he explained. "And I think that once we understand those key pathways, then we'll be able to both diagnose and treat cancers in the way that we thought was only remotely possible 25 years ago."

—Sharon Reynolds

Table of Links

1 http://edrn.nci.nih.gov
2 http://www.ncbi.nlm.nih.gov/pubmed/2024123
3 http://www.ncbi.nlm.nih.gov/pubmed/1566048
4 http://www.ncbi.nlm.nih.gov/pubmed/18413733
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