A Look at the Origins of Cancer Epigenetics

After discovering altered DNA methylation in cancer 30 years ago, researchers reflect on the field

In the era of federally funded large-scale epigenomic consortia, it may be hard to remember that until 30 years ago, when the first studies were published showing that DNA methylation was altered in human tumors, scientists didn't know that distinct epigenetic changes occur in cancer.

As a postdoc in the early 1980s, Andrew Feinberg, MD, MPH, now the director of the Center for Epigenetics at Johns Hopkins University School of Medicine in Baltimore, MD, studied slime mold differentiation. He thought that the epigenetic processes that allowed slime molds to differentiate and retain a memory of their intended cell type could be relevant to cancer, given that many scientists at the time had begun to consider cancer a disease of altered differentiation.

To test this idea, he teamed up with Bert Vogelstein, MD, now director of Hopkins's Ludwig Center for Cancer Genetics and Therapeutics. The pair decided to test whether levels of 5-methylcytosine, a modified base identified in mammalian DNA decades earlier, were altered in human tumors.

5-methylcytosine was "the only epigenetic change that was known at the time, so it's not like we had a lot of choices about what to study," notes Vogelstein. "From the perspective of someone who's a geneticist, who only knows how to look at DNA, it made sense to look at DNA methylation."

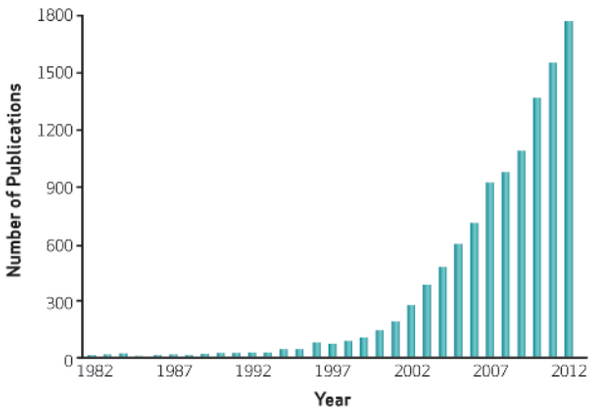
Looking at methylation-specific restriction enzyme cleavage patterns at specific genes, Feinberg and Vogelstein found that tumors had lower levels of DNA methylation than matched normal tissue, and they published their findings in January 1983 (Nature 1983;301:89–92).

"We saw dramatic differences in DNA methylation, so it was very, very striking," Feinberg recalls. "I remember how excited we were."

The effect of DNA methylation on gene expression was not yet clear, but "DNA hypomethylation was in a lot of tumor types; we found it pretty consistently," adds Vogelstein. "But you couldn't say for sure whether it was a cause or an effect of the neoplastic process, which was even more difficult then because you didn't know the genes involved."

Melanie Ehrlich, PhD, now professor in the Hayward Human Genetics Program at Tulane Cancer Center and of bioinformatics and genomics at Tulane University School of Medicine in New Orleans, LA, was also interested in DNA methylation. Originally fascinated by the complex DNA modifications in bacteriophages, Ehrlich had previously shown that humans had tissue-specific differences in genomic 5-methylcytosine levels. Later that year, Ehrlich and the late Charles Gehrke, PhD, found decreased 5-methylcytosine levels in a wide array of tumors.

Reaction to the teams' discoveries was mixed. "There was a lot of resistance," comments Ehrlich. "'Epiphenomenon' was one of the favorite put-downs." One agency, Feinberg says, even threatened to cut off his funding.



The number of published papers related to cancer epigenetics has skyrocketed over the past 30 years. Values are derived from a PubMed search for the terms "cancer" and "epigenetic."

Yet some cancer researchers took a chance on studying DNA methylation. Stephen Baylin, MD, now deputy director of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, discovered in 1986 that human cancers also harbored focal *hyper*methylation events. But it was not until the first tumor suppressor gene, retinoblastoma 1 (*RB1*), was cloned in 1987 and loss of *RB1* expression was linked to increased promoter hypermethylation in some tumors 2 years later that the idea that epigenetic changes contribute to tumorigenesis began to gain widespread acceptance.

The field has since exploded. Researchers have identified many additional epigenetic modifications involving DNA, histones, and nucleosomes, and have initiated large-scale projects to map genome-wide epigenetic marks in human cancers. Moreover, the identification of recurrent mutations in genes encoding DNA methyltransferases and chromatin remodeling proteins has lent credence to the idea that epigenetic events can drive tumorigenesis.

However, although most now feel that epigenetic changes are akin to genetic mutations and not a mere consequence of oncogenic transformation, some say evidence is still lacking. Timothy Bestor, PhD, professor of genetics and development at Columbia University Medical Center in New York, NY, who cloned the first mammalian DNA methyltransferase, recently received a Provocative Questions grant from the National Cancer Institute to test alternatives to the dogma that *de novo* methylation inactivates tumor suppressor genes.

Bestor finds today's resistance to questioning whether epigenetic changes drive cancer ironic, given how the early reports of altered methylation in cancer were received. "Everyone dismissed it when it came out, but now everyone says that they knew it all along," he says.

Greater proof that epigenetic changes contribute to cancer may come from ongoing clinical trials of modulators of DNA methylation and histone modifications.

Although he is pleased that history has been kind to the early work on DNA methylation in cancer, Baylin says, "I won't be ultimately gratified until I see something that really changes the management of cancer." –*Elizabeth McKenna* ■

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