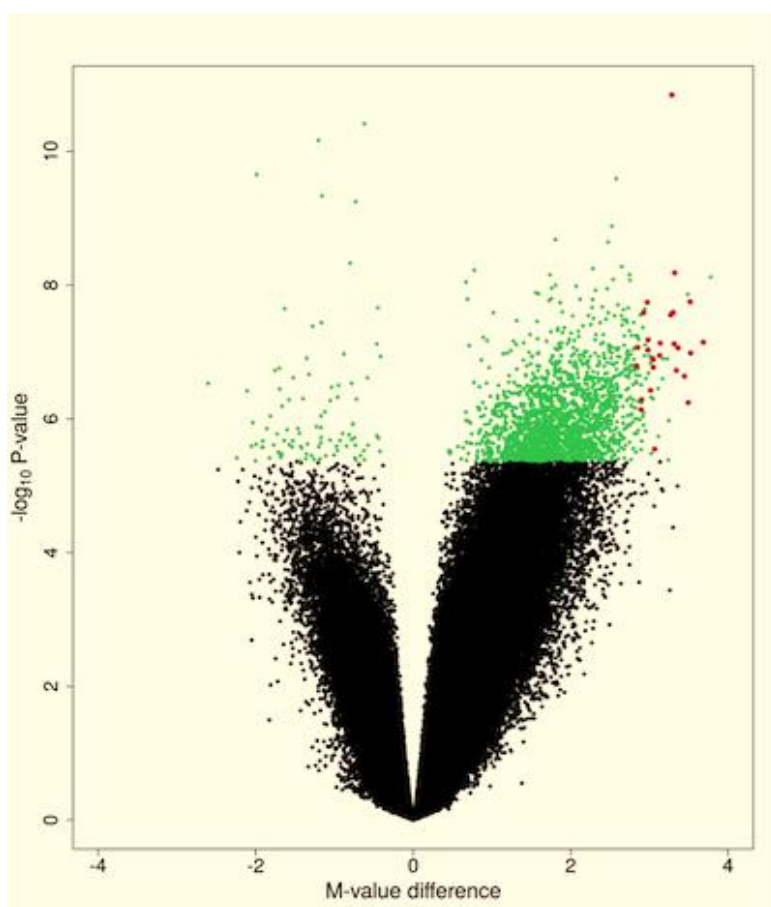


Beyond the genome: epigenetic changes specific to prostate tumors

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Volcano plot of DNA methylation in prostate cancer versus adjacent benign tissue. Differentially methylated CpGs are labeled in green or red. The 27 red-labeled CpG sites had a mean methylation difference of at least 40% between cancer and benign tissue; all were hypermethylated.

Image provided by Dr. Milan Geybels

Methylation of DNA is a well-known epigenetic mechanism for the control of gene expression. Methylation commonly occurs at CpG sites, or regions of DNA where a cytosine nucleotide occurs next to a guanine nucleotide. These sites tend to cluster into islands and are often found in gene promoter regions. CpG islands are typically unmethylated, thus allowing for uninhibited transcription of the gene, while hypermethylation of these regions can lead to transcriptional silencing. Losses and gains of DNA methylation have been associated with various cancers, including prostate cancer.

While previous research has investigated methylation in relation to prostate cancer, the majority of studies have examined methylation in only a select number of genes. To address this caveat, Drs.

Milan Geybels, Janet Stanford, and colleagues (Public Health Sciences Division) evaluated DNA methylation changes epigenome-wide in paired prostate cancer and adjacent benign tissue samples. This work, recently published in *The Prostate*, aimed to discover novel differences in methylation between cancerous and benign tissue samples and determine if previous findings from smaller studies would replicate in their larger study.

Paired samples came from 20 radical prostatectomy patients, 18 European Americans and 2 African Americans. The authors conducted epigenome-wide profiling and found over 2,000 CpG sites with differential DNA methylation; the majority of these CpGs were hypermethylated in cancer versus benign tissue. The average hypermethylation difference was 26%.

For verification of their results, the authors examined the 27 top-ranked differentially methylated CpG sites in 46 participants from the prostate cancer dataset in The Cancer Genome Atlas (TCGA). Confirming their initial findings, all 27 CpG sites were significantly hypermethylated in the cancerous tissue using TCGA. Next, the authors evaluated gene expression levels of these hypermethylated top-ranked regions. Of the 18 genes that had transcript data available, three genes (*SCGB3A1*, *HIF3A*, and *AOX1*) had reduced messenger RNA (mRNA) expression in cancer versus benign tissue.

Dr. Geybels describes the impact of this work, "we identified specific DNA methylation changes in prostate tumor tissue compared to non-cancer prostate tissue. These DNA methylation changes were in specific genes, some of which have not been implicated in prostate cancer before," such as *SCGB3A1*, a gene suggested to function as a tumor-suppressor. Furthermore, "we also confirmed some previous findings of genes that are differentially methylated in prostate cancer, thereby providing further evidence for a role of these genes in prostate carcinogenesis. Our findings may therefore provide new insights into the development of prostate cancer."

Additional Fred Hutch investigators contributing to this research were Shanshan Zhao, Chao-Jen Wong, and Dr. Michael Wu.

[Geybels MS, Zhao S, Wong C-J, Bibikova M, Klotzle B, Wu MC, Ostrander EA, Fan J-B, Feng Z, Stanford JL](#). 2015. Epigenomic profiling of DNA methylation in paired prostate cancer versus adjacent benign tissue. *Prostate*. 75(16):1941-50.

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