Study finds epigenetic similarities between Wilms tumor cells and normal kidney stem cells

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factors controlling when and in what tissues genes are expressed - of Wilms tumor reveals striking similarities to stem cells normally found in fetal kidneys. These findings by Massachusetts General Hospital (MGH) Cancer Center researchers have revealed new cellular pathways that are critical for Wilms tumor development and may also apply to other pediatric cancers. The report appears in the June 4 *Cell Stem Cell*.

Genetic mutations - changes to the sequence of DNA molecules - are known to underlie many types of cancer. But the role of epigenetics in tumor development is just beginning to be explored. The MGH team has been using advanced sequencing technology to investigate the role of chromatin, the structure that makes up chromosomes and consists of DNA wrapped around a protein backbone studded with molecules that can activate or suppress gene expression.

"An organism has only one genome, but it has many epigenomes because different cell types organize their genome into chromatin in ways that allow them to express just the right set of genes," explains Bradley Bernstein, MD, PhD, of MGH Pathology and the MGH Cancer Center, senior author of the study. Earlier studies from Bernstein's team used cutting-edge sequencing technologies to identify chromatin structures characteristic of embryonic stem cells. They observed active versions of chromatin structures termed "domains" at genes with critical developmental functions and saw features of both active and repressed

chromatin at "bivalent" genes that were not currently expressed but maintained the potential for activation.

For the current study, Bernstein teamed with Miguel Rivera, MD, and Daniel Haber, MD, PhD, of the MGH Cancer Center, along with Aviva Presser Aiden, PhD, of the Broad Institute, to apply those powerful genomic technologies to cancer. The researchers chose to examine the epigenetics of Wilms tumor, a kidney cancer that usually occurs in children, because pediatric cancer cells are likely to have few genetic alterations, making it easier to identify epigenetic changes.

Whole-genome chromatin screening of Wilms tumors, normal kidney tissues and fetal kidney tissues revealed that the chromatin of Wilms tumors contains the same types of active and bivalent chromatin structures identified in embryonic stem cells. Among the active genes were many well established regulators of kidney development, as well as a new set of genes that may be critical in tumor development. The presence of bivalent genes shows that normal developmental programs had been interrupted at an early stage in the tumor cells. In essence, Wilms cells give rise to a tumor by indefinitely continuing to behave like renal stem cells.

While surgical removal and chemotherapy are successful for the majority of patients with Wilms tumor, current treatment protocols fail in up to 15 percent of patients, notes Rivera, who is co-lead author of the *Cell Stem Cell* report. "Epigenetic analysis has provided an unprecedented level of detail on the biology of Wilms tumor, allowing us to identify new genes that are likely to be important in this disease and to pinpoint specific defects in developmental pathways. Both of these findings may provide new avenues for therapy," he says. Rivera is an assistant professor of Pathology, and Bernstein an associate professor of Pathology at Harvard Medical School.

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