

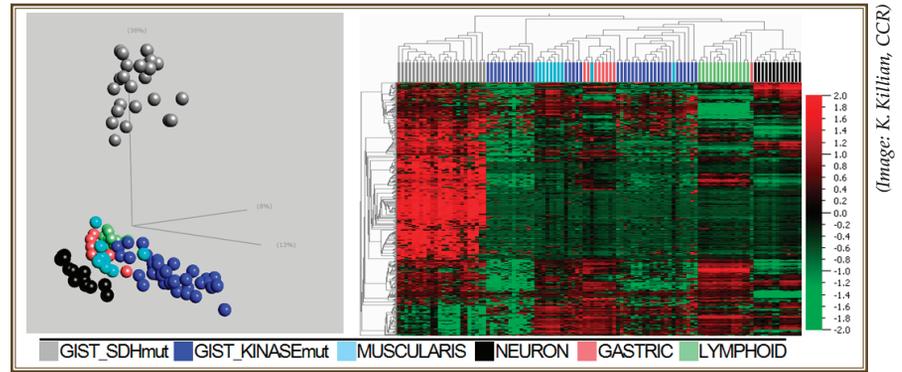
# The GIST of One Cancer: Two Distinct Molecular Diseases

*New results from the pediatric GIST program find that radically different epigenetic patterns define rare disease subtypes.*

Most adults with gastrointestinal stromal tumors (GIST) have mutations in one of the known cancer signaling pathways—usually in the gene for the receptor tyrosine kinase, KIT—that both drive the disease and render it vulnerable to targeted drugs. However, other patients—usually children and younger adults—have tumors that lack such obvious genetic causes and historically, were simply described as wildtype GIST. In a recent issue of *Cancer Discovery*, Keith Killian, M.D., Ph.D., Paul Meltzer, M.D., Ph.D., and their colleagues in CCR’s Genetics Branch, describe the identification of two distinct GIST categories based on patterns of DNA modifications. Their findings have implications that go beyond GIST itself to other cancer types.

Several years ago, CCR’s Scientific Director for Clinical Research, Lee Helman, M.D., set up the pediatric oncology program to study wildtype GIST by bringing together patients with this mysterious disease under one clinical roof. The program’s multidisciplinary team of clinicians and pathologists discovered that a subset of GIST tumors harbored different mutations in the genes encoding subunits of succinate dehydrogenase (SDH), a key enzyme complex in the Krebs cycle, the backbone of aerobic energy production. SDH mutations affect mitochondrial metabolism, but their role in tumorigenesis is uncertain.

Looking beyond mutations in the primary sequence of tumor DNA, Killian and colleagues wondered whether epigenetic DNA modifications—key arbiters of gene expression that help to define cellular



(Image: K. Killian, CCR)

Unsupervised principal component analysis (left) and 2D hierarchical clustering (right) of genomic methylation profiles reveal that SDH-mutant GIST possess a characteristic, unifying epigenomic divergence from kinase-mutant GIST and normal tissues.

type—could be playing a critical role in the disease. By studying the patterns of one such modification—methylation—they found that GIST was clearly separable into two forms: one in which the pattern of DNA methylation resembled surrounding and related tissues, and the other in which there was a profound increase in methylation observed over hundreds of genetic loci accompanied by a more restricted but equally distinct hypomethylation. The latter pattern included tumors with all known SDH mutations.

Mutations in SDH result in an accumulation of succinate, which itself acts as an inhibitor of several enzymatic reactions, some of which are involved in the maintenance of DNA methylation. With that in mind, Meltzer’s team looked at the methylation patterns in tumors from other types of cancers with similar metabolic abnormalities, e.g., paragangliomas associated with SDH mutations and gliomas associated with mutations of the isocitrate dehydrogenase gene (IDH). They found the same

striking pattern of predominant hypermethylation associated with these very different cancers.

The researchers neither know how these epigenetic changes are related to the cancer phenotype, nor do they know exactly how the metabolic alterations lead to changes in DNA methylation, although they are following evidence that suggests that inhibition of the cells’ ability to remove methylation is at play.

“When we started the GIST clinical program, we didn’t even know if we had a true subset of the disease,” said Meltzer. “So our work represents some real progress in the classification of these patients, which should eventually lead to improved care. These patients have also led us unexpectedly to the fascinating intersection of cancer genetics, epigenetics, and metabolism.”

To learn more about Dr. Meltzer’s research, please visit his CCR Web site at <http://ccr.cancer.gov/staff/staff.asp?name=pmeltzer>.