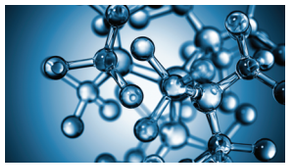
Drug Discovery

Major finding: The discovery of a selective PI3Kγ inhibitor reveals a role for PI3Kγ in T_H17 cell function.

Mechanism: CZC24832 suppresses RORγt expression and reduces the number of IL-17A–producing cells.

Impact: Selective PI3Kγ inhibition may impair the activity of tumor-associated T_H17 cells.

PI3Kγ REGULATES T_H17 CELL DIFFERENTIATION



The class I phosphoinositide 3-kinases (PI3K) are attractive targets for antitumor therapy, but selective targeting of PI3K isoforms has been hampered by the close structural similarities among the PI3Ks and other lipid kinases. Bergamini and colleagues developed a strategy to identify compounds that selectively inhibit PI3Kγ, a PI3K isoform that has previously been linked to inflammation. Briefly, compound libraries were screened in cell extracts for their ability to compete with a matrix of nonspecific PI3K and lipid kinase inhibitors, and matrix-bound proteins were eluted and spotted onto a nitrocellulose membrane to allow high-throughput detection of compounds that reduced PI3Kγ binding to the inhibitor matrix. A highly selective and potent ATP-competitive PI3Kγ inhibitor, CZC24832, was identified with suitable pharmacokinetic properties and oral bioavailability that suppressed inflammatory responses in mouse models in a dose-dependent manner. The authors treated primary human immune cells exposed to inflammatory signals with CZC24832 and found that T-cell interleukin 17A (IL-17A) production was strongly inhibited. Because IL-17A production is a hallmark of the distinct subset of $CD4^+$ helper T cells known as T_H17 cells, the authors tested the effect of CZC24832 on T_H17 cell differentiation. CZC24832 reduced expression of retinoic acid receptor–related orphan receptor γt (RORγt), a transcription factor that drives T_H17 differentiation, and decreased the number of IL-17A–producing cells. Importantly, both PI3Kγ and T_H17 cells have been implicated in the recruitment of inflammatory cells to tumors that can promote angiogenesis, immunosuppression, and tumor growth. Selective inhibition of PI3Kγ may therefore be a useful strategy to target tumor inflammation. ■

Bergamini G, Bell K, Shimamura S, Werner T, Cansfield A, Müller K, et al. A selective inhibitor reveals PI3Kγ dependence of T_H17 cell differentiation. Nat Chem Biol 2012 Apr 29 [Epub ahead of print].

Epigenetics

Major finding: Colon cancers are distinguished by epigenetic changes at a common set of enhancers.

Concept: Genes associated with variant enhancer loci are aberrantly expressed in colorectal cancer.

Impact: Genome-wide epigenetic enhancer deregulation may drive a pathogenic transcriptional program.

VARIANT ENHANCER LOCI PREDICT GENE DYSREGULATION IN COLON CANCER

Genome-wide epigenetic changes that affect chromatin structure at gene promoters are known to occur in tumor cells, but cancer-specific alterations at enhancers have been relatively uncharacterized. Enhancers are *cis*-regulatory elements that mediate long-range regulation of gene expression and are marked by monomethylation of lysine 4 on histone H3 (H3K4me1). To identify differences in enhancer activity between normal and cancer cells, Akhtar-Zaidi and colleagues performed H3K4me1 chromatin immunoprecipitation followed by DNA sequencing on normal intestinal crypts and colorectal cancer cell lines derived from early-stage tumors, late-stage tumors, and liver metastases. Thousands of H3K4me1 sites were differentially lost or gained in the colorectal cancer samples compared with the normal crypts, and many variant enhancer loci were shared across multiple independent colorectal cancer cell lines. To determine the impact of these loci in colorectal cancer, the authors analyzed the expression of enhancer-associated genes and found that genes linked to gained enhancers generally had a higher level of expression in colorectal cancer cells than in normal crypts, and genes regulated by lost enhancers had lower expression in colorectal cancer cells than crypts. Importantly, these genes were also found to be aberrantly expressed in primary tumors, suggesting that variant enhancer loci constitute a signature that predicts the colorectal cancer transcriptome. Additionally, of the 20 single-nucleotide polymorphisms that have so far been identified by genome-wide association studies to confer colorectal cancer risk, 80% overlapped at least one H3K4me1 site in the colon crypt. Together, these results suggest that a common epigenetic enhancer signature contributes to the colorectal cancer phenotype and provide further evidence that disease-associated variants may impair the function of tissue-specific enhancers. ■

Akhtar-Zaidi B, Cowper-Sal Lari R, Corradin O, Saiakhova A, Bartels CF, Balasubramanian D, et al. Epigenomic enhancer profiling defines a signature of colon cancer. Science 2012;336:736–9.