Leukemia

Major finding: AML-associated DNMT3A R882H mutants exert dominant-negative effects leading to hypomethylation.

Mechanism: R882H mutants heterodimerize with WT DNMT3A and prevent the formation of active WT homotetramers.

Impact: R882 and non-R882 *DNMT3A* mutations may contribute to AML through distinct mechanisms.

DNMT3A R882H MUTANTS DOMINANTLY INHIBIT ACTIVE DNMT3A TETRAMERS IN AML

Heterozygous *DNMT3A* mutations affecting R882 within the methyltransferase catalytic domain account for approximately 60% of *DNMT3A* mutations in acute myeloid leukemia (AML), which are commonly found in patients with normal karyotype AML (NK-AML). These mutations reduce *de novo* DNA methylation *in vitro*, but the underlying mechanism is unclear. Russler-Germain and colleagues utilized a cohort of 80 NK-AML patient samples in order to further explore the impact of R882 alleles on wild-type (WT) DNMT3A methyltransferase activity. Allele frequency and mass spectrometry analysis revealed that *DNMT3A* R882 mutations were typically heterozygous, originated in NK-AML founder clones, and were expressed to the same extent as the WT allele. In addition, heterozygous R882-mutant samples showed a small but statistically significant reduction in genome-wide methylation compared with WT that was not seen in non-R882 *DNMT3A*-mutant samples. Hypomethylation profiles were nearly identical in NK-AMLs harboring R882H, the most common R882 mutation, as well as R882C mutants. Furthermore, hypomethylation at specific CpGs was correlated with expression changes of associated genes, although genes were both up- and downregulated. Although mixing recombinant WT and R882H DNMT3A *in vitro* did not affect WT DNMT3A enzymatic activity, coexpression of WT and R882H DNMT3A in human cells resulted in an 80% reduction in methyltransferase activity compared with WT DNMT3A alone, confirming that the R882H mutant possesses dominant-negative activity. The R882H mutant proteins did not inhibit WT DNMT3A activity by affecting subcellular localization or modifying CpG substrate specificity, but rather formed heterodimers with WT DNMT3A that inhibited the formation of active WT homotetramers. The finding that R882 DNMT3A mutants specifically confer a hypomethylation phenotype by inhibiting DNMT3A activity in a dominant-negative manner raises the possibility that R882 and non-R882 DNMT3A-mutant AML may be etiologically distinct. ■

Russler-Germain DA, Spencer DH, Young MA, Lamprecht TL, Miller CA, Fulton R, et al. The R882H DNMT3A mutation associated with AML predominantly inhibits wild-type DNMT3A by blocking its ability to form active tetramers. Cancer Cell 2014 Mar 20 [Epub ahead of print].

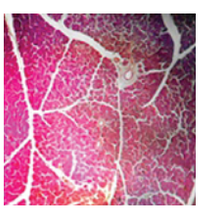
Pancreatic Cancer

Major finding: Mass transport features of pancreatic tumors are associated with gemcitabine delivery and response.

Approach: Intraoperative infusion allowed correlation of drug uptake with CT-determined transport properties.

Impact: Mass transport analysis can be integrated into standard diagnostic tests and may have prognostic value.

PANCREATIC TUMOR TRANSPORT PROPERTIES AFFECT GEMCITABINE UPTAKE AND EFFICACY



Structural abnormalities in solid tumors, including disorganized or leaky blood vessels, increased stromal density, or dysfunctional transport proteins, can alter mass transport properties and thereby impair delivery of therapeutic agents. Hypothesizing that such physical features may negatively affect the delivery and effectiveness of the nucleoside analogue gemcitabine in patients with pancreatic ductal adenocarcinoma (PDAC), Koay and colleagues developed a computed tomography (CT)–based mathematical model describing mass transport based on properties of the pancreatic tissue and surrounding vasculature in 176 pretherapy pancreatic CT scans and determined whether tumor transport properties were associated with gemcitabine incorporation in a first-in-kind prospective clinical trial in which 12 patients with PDAC received gemcitabine intravenously during curative surgical resection. Overall, tumors showed reduced transport compared with normal pancreatic tissues, and among 110 patients who had received gemcitabine-based therapy and had evaluable pretherapy CT scans, decreased transport was associated with poor response to therapy and reduced overall survival. In the 12 patients enrolled in the trial, gemcitabine incorporation in both normal and malignant pancreatic tissue was highly variable, with structural features at both the cellular and molecular levels influencing gemcitabine uptake; after controlling for expression of equilibrative nucleoside transporter 1 (ENT1), which transports gemcitabine across the cell membrane, gemcitabine incorporation inversely correlated with the amount of stroma. Moreover, as predicted, the mass transport parameters derived by applying the mathematical model to the patients' pretherapy CT scans were correlated with the tumor stromal score and inversely correlated with gemcitabine incorporation. Although further studies are needed to assess whether CT-determined transport parameters are predictive of gemcitabine incorporation and efficacy, these results suggest that the structural features and transport properties of PDAC determine gemcitabine effectiveness and provide a rationale for integration of mass transport analysis into diagnostic testing. ■

Koay EJ, Truty MJ, Cristini V, Thomas RM, Chen R, Chatterjee D, et al. Transport properties of pancreatic cancer describe gemcitabine delivery and response. J Clin Invest 2014;124:1525–36.