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Personalized Medicine

Major finding: Patients with *PIK3CA* mutations are more responsive to PI3K/AKT/mTOR inhibitors.

Approach: PI3K/AKT/mTOR inhibitors were given to patients with advanced PIK3CA-mutant cancers.

Impact: Screening for PIK3CA mutations may guide treatment of breast and gynecologic cancers.

PIK3CA MUTATIONS PREDICT RESPONSE TO PI3K/AKT/MTOR INHIBITORS

Mutations in the p110α subunit of phosphatidylinositol 3-kinase (PI3K), encoded by *PIK3CA*, are common in breast and gynecologic malignancies. Preclinical studies have suggested that *PIK3CA* mutations, which activate the PI3K/AKT/mTOR pathway, respond to treatment with PI3K and mTOR inhibitors. In a prospective clinical trial, Janku and colleagues sequenced *PIK3CA* in tumor samples from patients with advanced breast, cervical, endometrial, and ovarian cancers that were refractory to standard therapies and referred to the Clinical Center for Targeted Therapy (Phase I Program) at The University of Texas MD Anderson Cancer Center. Of the 140 patients analyzed, 25 (18%) were positive for *PIK3CA* mutations, and 23 of these patients were then enrolled in a clinical trial that included a PI3K/AKT/mTOR pathway inhibitor. A partial response was observed in 30% of the patients harboring a *PIK3CA* mutation. In contrast, only 10% of patients with wild-type *PIK3CA* who were treated on the same protocols and had the same disease types responded to treatment. The authors also tested 81 of these patients for simultaneous mitogen-activated protein kinase pathway mutations, which may mediate resistance to PI3K/AKT/mTOR inhibitors, and found a significant association between the presence of *RAS* (*KRAS* or *NRAS*) or *BRAF* mutations and *PIK3CA* mutations. Importantly, 2 of 7 patients with coexisting mutations responded to targeted therapy. Although the overall number of patients included in these studies was small, the findings suggest that *PIK3CA* mutations are common in patients with advanced breast and gynecologic cancers. Screening for *PIK3CA* mutations may reveal a subset of patients who are sensitive to treatment regimens that include a PI3K/AKT/mTOR inhibitor. ■

Janku F, Wheler JJ, Westin SN, Moulder SL, Naing A, Tsimberidou AM, et al. PI3K/AKT/mTOR inhibitors in patients with breast and gynecologic malignancies harboring PIK3CA mutations. J Clin Oncol 2012 Jan 23. [Epub ahead of print].

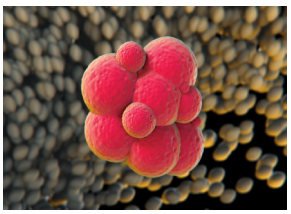
Stem Cells

Major finding: Stem cells and committed progenitors can both initiate tumors in HOXA9-MEIS1 AML.

Concept: HOXA9-MEIS1-induced leukemic expansion defies the strict hematopoietic hierarchy.

Impact: A specific immunophenotype does not dictate cancer "stemness."

TUMOR-INITIATING ACTIVITY IS INDEPENDENT OF IMMUNOPHENOTYPE



It remains unclear whether acute myeloid leukemia (AML) is initiated by a specific population of stem cells within a tumor or if cells with a more differentiated phenotype are equally capable of establishing and maintaining the leukemic state. To better understand the nature of tumor-initiating activity, Gibbs and colleagues purified distinct blood cell populations from mice with HOXA9-MEIS1–driven AML and tested their individual ability to initiate disease in secondary recipients. Unexpectedly, cells immunophenotypically resembling hematopoietic stem/progenitor cells as well as committed lymphoid and myeloid progenitors had tumor-initiating activity, and each cell compartment could recapitulate the entire immunophenotypic spectrum of AML following serial transplantation. This observation indicated that the cells with a more differentiated phenotype could give rise to immunophenotypically less differentiated cells or cells of a different lineage, suggesting that HOXA9-MEIS1 induces a dynamic tumorigenic hierarchy that does not adhere to the strict bounds of normal "forward" hematopoiesis. Unsupervised hierarchical clustering of gene expression data revealed that the tumor-initiating cells in HOXA9-MEIS1 primary AML most closely resembled normal hematopoietic stem cells, and a single-cell analysis of tumor-initiating cells using mass cytometry showed that certain common pathways were activated in the distinct tumor-initiating cell populations. The individual tumor-initiating cell populations were also similarly sensitive to inhibition of MEK, DNA methyltransferases, and PI3K *in vitro*. Inhibition of these shared signaling nodes, but not pathways whose activation varied among the tumor-initiating cell populations, significantly increased survival of HOXA9-MEIS1 AML mice. Although the identification of tumor-initiating cells that establish and maintain hierarchical tumor organization supports the cancer stem cell hypothesis, these findings also suggest that "stemness" in AML can be a phenotypically dynamic, pharmacologically targetable state shared by multiple cell types. ■

Gibbs KD, Jager A, Crespo O, Goltsev Y, Trejo A, Richard CE, et al. Decoupling of tumor-initiating activity from stable immunotype in Hoxa9-Meis1-driven AML. Cell Stem Cell 2012;10:210–17.

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CANCER DISCOVERY

Tumor-Initiating Activity Is Independent of Immunophenotype

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