Leukemia

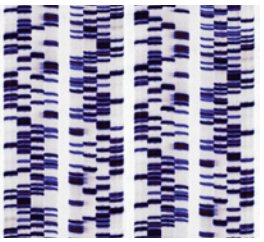
Major finding: Genetic lesions associated with relapsed ALL converge on WNT and MAPK pathways.

Approach: Three high-throughput analyses were performed on bone marrow samples from patients with ALL.

Impact: Therapeutic strategies for relapsed ALL should target relapse-specific genetic events.

GENOMIC ANALYSIS OF RELAPSED ACUTE LEUKEMIA

Acute lymphoblastic leukemia (ALL) is the most common type of childhood cancer, characterized by overproduction of immature malignant white blood cells in the bone marrow. Although the cure rate is relatively high, prognosis tends to be poor for relapses, which are often chemoresistant. To better characterize genetic changes associated with relapse, Hogan and colleagues analyzed gene expression, copy number abnormalities (CNA), and DNA methylation of matched diagnosis/relapse bone marrow samples from children with relapsed B-precursor ALL. Gene expression profiling revealed a different gene signature in patients with early versus late relapse, with genes involved in nucleotide biosynthesis and folate metabolism specifically up-regulated at late relapse. CNA analysis identified copy number changes mostly shared between diagnosis and relapse in the same patient, and DNA methylation showed a distinctly higher CpG methylation level at relapse versus diagnosis. To pinpoint a common



relapse-driving genetic event, the authors then used cross-platform integration to compare all three genomic profiles. *CDKN2A*, *CSMD1*, *PTPRO*, and *COL6A* were significantly different between diagnosis and relapse in all three assays and have been found to be either epigenetically silenced or to act as tumor suppressors in multiple cancers, excluding *COL6A*. Further analysis revealed convergence of the genetic changes on the WNT/β-catenin and mitogen activated protein kinase (MAPK) signaling pathways, two biologically relevant pathways in cancer. Overall, the data forward our understanding of the key genetic events that drive the timing and occurrence of relapsed ALL, as well as inform the identification of novel therapeutic targets. ■

Hogan LE, Meyer JA, Yang J, Wang J, Wong N, Yang W, et al. Integrated genomic analysis of relapsed childhood acute lymphoblastic leukemia reveals therapeutic strategies. Blood. 2011 Sept 14. [Epub ahead of print]

Imaging

Major finding: Fluorescently labeled folate can identify tumor masses <1 mm during surgery.

Concept: The vast majority of epithelial ovarian cancers overexpress folate receptor-α (FR-α).

Impact: Real-time imaging with cancer-specific agents can improve tumor staging and excision.

INTRAOPERATIVE IMAGING IMPROVES OVARIAN CANCER DETECTION

Epithelial ovarian cancer (EOC) is the most lethal gynecologic malignancy, and is often not diagnosed until advanced stages. Because the most effective treatment for this cancer remains cytoreductive surgery followed by chemotherapy, improved tumor detection would aid debulking efforts and potentially prolong survival. Recent studies have suggested that folate receptor-α (FR-α) is specifically overexpressed in EOC compared to healthy ovarian tissue and is therefore a potentially useful target for imaging. van Dam and colleagues hypothesized that this characteristic of EOC could be exploited through the use of systemically administered fluorescin isothiocyanate (FITC)–conjugated folate, which binds FR-α and is internalized into ovarian cancer cells. In a proof-of-principle study of 10 ovarian tumors, they demonstrate that folate-FITC–labeled tumor cells can be distinguished from surrounding normal tissue with a multispectral fluorescence camera during surgery. Real-time fluorescent labeling enabled surgeons to detect a significantly higher number of tumor masses—some smaller than 1 mm—than visual inspection alone. Histopathology confirmed that the fluorescence was restricted to malignant, FR-α–positive tissues. Furthermore, intravenously injected folate-FITC was safely administered, and the tumor-specific signal persisted up to 8 hours after injection to allow tumor detection during long surgical procedures. However, this approach would not be applicable to the 5% to 10% of EOC cases that do not overexpress FR-α. FR-α is also not uniformly overexpressed in other solid tumors, although preoperative tests may be performed to identify candidates for intraoperative folate imaging. More clinical studies are required to determine if this procedure impacts survival of women with malignant, FR-α–positive EOC, but the improvement of tumor detection to submillimeter size will facilitate tumor cytoreduction and allow more accurate staging of cancers. ■

van Dam GM, Themelis G, Crane LM, Harlaar NJ, Pleijhuis RG, Kelder W, et al. Intraoperative tumor-specific fluorescence imaging in ovarian cancer by folate receptor-α targeting: first in-human results. Nat Med. 2011 Sept 18. [Epub ahead of print]

Note: *Research Watch* is written by *Cancer Discovery* Science Writers. Readers are encouraged to consult the original articles for full details.

CANCER DISCOVERY

Genomic Analysis of Relapsed Acute Leukemia

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