Targeted Therapy

Major finding: SHH-subgroup medulloblastomas are genetically distinct in infants, children, and adults.

Concept: Unlike adult tumors, many infant and childhood SHH medulloblastomas have mutations downstream of SMO.

Impact: Tumor genetics should be used to stratify patients with SHH-subgroup medulloblastoma for therapy.

GENETIC MUTATIONS PREDICT SMO INHIBITOR RESPONSE IN SHH MEDULLOBLASTOMA

Medulloblastoma can be classified into multiple subtypes that differ in cell histology, biology, and clinical phenotype. Although surgery, radiation, and chemotherapy can be curative, long-term side effects are common, necessitating the development of less toxic targeted therapies. Inhibitors of Smoothened (SMO), a regulator of the sonic hedgehog (SHH) pathway, are of particular interest given that one medulloblastoma subgroup is distinguished by SHH pathway activation. However, clinical responses to SMO inhibitors have been varied, potentially due to mutations in SHH genes that act downstream of SMO. To determine whether the genetic landscape of SHH-subgroup medulloblastoma might suggest predictors of SMO inhibitor sensitivity, Kool and colleagues performed genomic profiling of 50 adult, 33 childhood, and 50 infant SHH medulloblastomas and observed that DNA methylation and gene expression profiles and the number of somatic mutations largely clustered according to age. Surprisingly, although SHH pathway genes were mutated in 116 of 133 (87%) tumors, mutations other than *PTCH1* were associated with certain age groups. *SUFU* mutations were almost exclusively found in infants, whereas *SMO* mutations were most common in adults. Children with SHH medulloblastoma rarely had *SUFU* or *SMO* mutations, but often harbored *TP53* germline mutations accompanied by chromothripsis-associated *GLI2* and *MYCN* amplification. *TERT* promoter mutations were also almost exclusively found in adult SHH medulloblastomas, and the PI3K–AKT–mTOR pathway was more frequently activated in adult tumors. Cells harboring mutations in *PTCH1*, which acts upstream of SMO, but not *TP53*, *MYCN*, or *SUFU*, which act downstream of SMO, were sensitive to NVP-LDE225, a SMO inhibitor currently being tested in phase III clinical trials, suggesting that some infant and childhood SHH medulloblastomas may be intrinsically resistant to SMO inhibition. The finding that SHH medulloblastoma is genomically distinct in different age groups emphasizes the importance of using underlying SHH mutations to stratify patients for therapy. ■

Kool M, Jones DT, Jäger N, Northcott PA, Pugh TJ, Hovestadt V, et al. Genome sequencing of SHH medulloblastoma predicts genotype-related response to Smoothened inhibition. Cancer Cell 2014;25:393–405.

Mouse Models

Major finding: AML subclones can correspond to distinct cell populations with different functional capacities.

Concept: Rare subclones can preferentially engraft in immunodeficient mice and skew the clonal architecture.

Impact: Tumors should be genomically characterized before and after xenotransplantation.

AML SUBCLONES CAN BE FUNCTIONALLY AND PHENOTYPICALLY DISTINCT

Intratumoral heterogeneity arises during tumor evolution as subpopulations of cells acquire additional mutations that were not present in the initial founding clone. Functional heterogeneity can also exist among primary tumor cells, but the relationship between functional heterogeneity and clonal organization within tumors is unclear. Klco and colleagues performed whole-genome sequencing of bone marrow cells from 19 patients with *de novo* acute myeloid leukemia (AML) and identified founding clones and leukemic subclones based on the variant allele fraction of somatic mutations. All subclones were present in corresponding peripheral blood samples, suggesting that different AML subclones have an equal propensity to peripheralize. However, some AML subclones corresponded to morphologically distinct leukemic cell populations, such as monocytes or blasts, indicating that subclones can differ in their capacity for differentiation. Some AML subclones also had different growth properties, with some primary AML samples retaining their original clonal organization after being cultured on stromal cells, and others showing substantial enrichment of individual subclones. Consistent with these findings, sequencing of patient-derived AML bone marrow xenografts showed preferential engraftment of individual subclones, many of which were only minor subclones in the primary AML sample and were not predominant in patients at relapse. In some cases, subclone engraftment was dependent on the mouse strain used, and the immunophenotype of the predominant subclone could be affected by the cytokine milieu of the host. Importantly, this preferential engraftment led to significant subclonal restriction, with many xenografts composed of only a single subclone and none maintaining the exact clonal organization as the primary AMLs from which they were derived. In addition to demonstrating that tumor subclones arising from the same founding clone can be phenotypically and functionally heterogeneous, these findings caution against generalizing experimental data obtained from xenografts to parental tumors without performing genomic analyses before and after xenotransplantation. ■

Klco JM, Spencer DH, Miller CA, Griffith M, Lamprecht TL, O'Laughlin M, et al. Functional heterogeneity of genetically defined subclones in acute myeloid leukemia. Cancer Cell 2014;25:379–92.

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