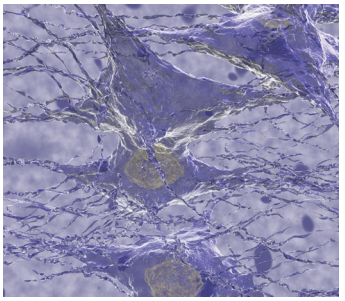
Glioma

Major finding: Oligodendrocyte precursor cells identified as glioma cell of origin.

Method: MADM used to follow entire tumorigenic process.

Significance: Cell of mutation and cell of origin can differ.

MADM IDENTIFIES OPC AS GLIOMA CELL OF ORIGIN



A cancer "cell of origin" is a specific cell type that can progress to a tumor due to a permissive signaling context that results from a set of particular genetic abnormalities. Better understanding of cell of origin should help determine tumor origin, identify mechanisms of tumorigenesis, predict tumor biology and behavior, and develop strategies for rational intervention. However, the cell of origin can be difficult to identify based on the heterogeneous cell population in late-stage patient tumors. Therefore, researchers have increasingly turned to mouse models to identify cell of origin. Now, Liu and colleagues have used mosaic analysis with double markers (MADM) to identify the cell of origin in a mouse model of glioma. The authors genetically inactivated *p53* and *NF1* in neural stem cells (NSC) labeled with green fluorescent protein and followed all NSC-derived lineages. They determined that oligodendrocyte precursor cells (OPC) were overrepresented in a "pretransforming" stage and maintained their proliferative capacity. Gliomas that eventually arose in these mice expressed OPC markers. Very interestingly, NSCs containing mutant *p53* and *NF1* did not show overexpansion, suggesting that the cell of mutation and cell of origin can differ. To confirm the ability of OPCs to transform, *p53* and *NF1* were inactivated only in this cell type, and mice developed tumors. These findings highlight the utility of MADM in following the entire tumorigenic process and precisely identifying cell of origin. Such knowledge should help in the design of effective drugs that target the vulnerability of signaling pathways in the cell of origin that are perturbed by particular genetic mutations. ■

Liu C, Sage JC, Miller MR, Verhaak RG, Hippenmeyer S, Vogel H, et al. Mosaic analysis with double markers reveals tumor cell of origin in glioma. Cell 2011;146:209–21.

Leukemia

Major finding: Aberrant epigenetic activity of the histone methyltransferase DOT1L causes MLL.

Impact: A selective inhibitor of DOT1L prevents expression of leukemogenic genes and increases survival in a mouse model of MLL.

Significance: Small molecule inhibition of histone methyltransferases may be a potential therapeutic option for diseases caused by aberrant epigenetic activity.

DOT1L IS A THERAPEUTIC TARGET IN MIXED-LINEAGE LEUKEMIA

Mixed lineage leukemia (MLL) is an aggressive form of leukemia that affects both infants and adults and typically carries a poor prognosis. The underlying genetic defect is a chromosomal translocation that fuses the *MLL* gene to a variety of partners, and the resulting oncogenic fusion proteins gain the ability to interact with at least 3 known protein complexes, one of which contains DOT1L, a histone methyltransferase that catalyzes the methylation of histone H3 (H3K79). The new association between DOT1L and the MLL fusion proteins results in DOT1L recruitment to aberrant gene locations. Previous studies of MLL-translocated leukemia have found enhancement of H3K79 methylation at MLL-fusion loci and hypothesized that DOT1L activity may activate and maintain MLL fusion-mediated gene expression. However, it remains unclear whether an epigenetic modification can regulate the transcription of a specific subset of leukemogenic genes. In a recent article, Bernt and colleagues investigated whether MLL fusion-mediated gene expression and leukemia maintenance depend on DOT1L. Using *MLL*-rearranged leukemia cells, the authors first identified MLL-fusion target loci and found them to be specifically associated with methylation of H3K79. Loss of Dot1l resulted in loss of H3K79 methylation, downregulation of MLL fusion target genes, and increased differentiation and apoptosis of leukemia cells. Dot1l also was necessary for the development of leukemia *in vivo*. Importantly, the discovery that the development and maintenance of *MLL*-rearranged leukemia is dependent upon a DOT1L-imposed aberrant epigenetic program suggests that DOT1L may be a potential therapeutic target for this disease. In a related article, Daigle and colleagues report the development of EPZ004777, a potent, selective inhibitor of DOT1L. Designed to sit in the catalytic active site of DOT1L, EPZ004777 specifically inhibited cellular H3K79 methylation, expression of MLL-fusion target genes, and proliferation of *MLL*-rearranged cells without affecting the proliferation of nontranslocated cells. In a mouse xenograft model of MLL, administration of EPZ004777 led to

an overall increase in survival in the absence of overt toxicity or severe hematopoietic side effects. Overall, these results provide strong evidence that small molecule inhibition of DOT1L represents a potential targeted therapeutic against *MLL*-translocated leukemia, a disease that currently has limited treatment options. ■

Daigle S, Olhava EJ, Therkelsen CA, Majer CR, Sneeringer CJ, Song J, et al. Selective killing of mixed lineage leukemia cells by a potent small-molecule DOT1L inhibitor. Cancer Cell 2011;20:53–65.

Bernt KM, Zhu N, Sinha AU, Vempati S, Faber J, Krivtsov AV, et al. MLL-Rearranged leukemia is dependent on aberrant H3K79 methylation by DOT1L. Cancer Cell 2011;20:66–78.

Radiotherapy

Major finding: Intermediate-risk group of patients with localized prostate cancer benefit from combined radiotherapy and short-term ADT.

Clinical outcome: Combined radiotherapy with ADT resulted in 10-year overall survival of 62%.

Future direction: Optimal radiation dose for these patients must be determined and longer follow-up may be required to observe benefits in patients with low-risk disease.

COMBINED RADIOTHERAPY AND ANDROGEN-DEPRIVATION THERAPY

External beam radiation therapy plus androgen-deprivation therapy (ADT) is standard of care for men with advanced localized adenocarcinoma of the prostate, and it has been suspected but not known whether this combined therapy would be effective among patients with early localized disease. Jones and colleagues report on a phase III study of 1,979 patients with early-stage prostate adenocarcinoma treated either with radiotherapy alone or radiotherapy plus ADT with a mean follow-up of 9.1 years. The addition of ADT was associated with an improvement in the primary endpoint, 10-year overall survival, from 57% to 62%. Secondary endpoints including disease-specific mortality, distant metastases, increasing prostate-specific antigen levels, and positive findings on repeat biopsies were also significantly improved. Risk analysis showed that improvements in overall survival and disease-specific mortality were seen primarily among intermediate-risk patients, with no significant reductions among low-risk patients. ■

Jones CU, Hunt D, McGowan DG, Amin MB, Chetner MP, Bruner DW, et al. Radiotherapy and short-term androgen deprivation for localized prostate cancer. N Engl J Med 2011;365:107–18.

Genomics

Major finding: Study reports on messenger RNA and microRNA expression, promoter methylation, and DNA copy number in high-grade serous ovarian adenocarcinomas.

Impact: Up to half of these cancers may have aberrations in genes involved in homologous recombination and thus benefit from PARP inhibitors.

Approach: Large-scale analysis of genomic aberrations identifies many genes as potential therapeutic targets.

INTEGRATED GENOMIC ANALYSIS OF OVARIAN CARCINOMA

Identification of disease-associated molecular alterations is critical for the development of targeted therapeutics. The Cancer Genome Atlas Research Network has reported on a large-scale analysis of messenger RNA and microRNA expression, promoter methylation, and DNA copy number in 489 high-grade serous ovarian adenocarcinomas. Nearly all high-grade serous ovarian carcinomas were found to have mutations in *p53* as well as several genes mutated at lower frequencies, including *CDK12*, a kinase involved in regulation of RNA splicing. Gene expression analysis identified 4 distinct subtypes of ovarian cancer. Pathway analyses suggest that homologous recombination is defective in about half of the tumors analyzed, and that NOTCH and FOXM1 signaling are involved in serous ovarian cancer pathophysiology. Additionally, 22 genes for which inhibitors already exist were identified in regions of recurrent amplification. ■

Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature. 2011, 474:609–15.

Note: *Research Watch* is written by *Cancer Discovery* Editors. Readers are encouraged to consult the articles referred to in each item for full details on the findings described.

DOT1L Is a Therapeutic Target in Mixed-lineage Leukemia

Cancer Discovery 2011;1:196-197.