Clinical Response of Carcinomas Harboring the BRD4–NUT Oncoprotein to the Targeted Bromodomain Inhibitor OTX015/MK-8628


Précis: Four patients with NMC harboring BRD4–NUT fusion protein were compassionately treated with the BET inhibitor OTX015/MK-8628, resulting in two rapid responses and one disease stabilization, and two patients achieved extended overall survival post-diagnosis.

DNMT3A Haploinsufficiency Transforms FLT3ITD Myeloproliferative Disease into a Rapid, Spontaneous, and Fully Penetrant Acute Myeloid Leukemia


Précis: In a mouse model harboring FLT3 internal-tandem duplication, DNMT3A haploinsufficiency disrupts methylation of methylation-sensitive genes, resulting in fully penetrant acute myeloid leukemia.

Tumor Cell–Driven Extracellular Matrix Remodeling Drives Haptotaxis during Metastatic Progression


Précis: An alternatively spliced form of the actin-associated protein MENA, MENAINV, associates with integrin α5β1 to induce migration toward high fibronectin concentrations and promote metastasis.

See commentary, p. 474
Chromosomal Instability Affects the Tumorigenicity of Glioblastoma Tumor-Initiating Cells .......................... 532


Précis: Glioblastoma tumor-initiating cells are a source of intratumor genetic heterogeneity due to chromosomal instability; however, further elevation of chromosomal instability results in reduced proliferation, self-renewal, and tumor-initiating properties in these cells.

PD-1hi Identifies a Novel Regulatory B-cell Population in Human Hepatoma That Promotes Disease Progression .................. 546


See commentary, p. 477

Godek and colleagues showed that glioblastoma tumor-initiating cells (TIC) are a source of genetic heterogeneity due to chromosomal instability (CIN). Glioblastoma TICs exhibited an increased frequency of lagging chromosomes at anaphase compared to stable diploid cells, and FISH analysis indicated that glioblastoma TICs exhibited high levels of aneuploidy, consistent with CIN. Further, TICs exhibited extensive karyotypic diversity, and p53 DNA-binding mutations resulted in aberrant p53 function, which may prevent growth arrest following mitotic defects. These results establish a critical link between TICs and CIN, which together may promote glioblastoma through functional and genetic heterogeneity. However, increased CIN beyond a tolerable upper limit resulted in reduced proliferation, suggesting a potential therapeutic vulnerability. For details, please see the article by Godek and colleagues on page 532.