

Highlights of This Issue

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CD44 Adhesion, Mechanosensing, and Motility

Kim *et al.* _____ Page 1416

Little is known about the biophysical contributions provided by the hyaluronic acid (HA) receptor CD44. In this study, Kim and colleagues combined HA-based engineered materials with genetic perturbation to demonstrate for the first time that CD44 directly participates in glioma cell mechanotransduction and invasive motility. Genomic and mechanistic evidence supports a new adhesion model in which CD44 provides early adhesive contacts that are later replaced by more robust integrin-based adhesions. Given the increasing use of HA as a materials scaffold, this work brings new molecular insight to the role of CD44 in cancer cell invasion and broadens the understanding of cell-material interactions.

Downstream Regulation by PcG in HCC

Gao *et al.* _____ Page 1388

Polycomb-group (PcG) proteins are evolutionarily conserved and often associated with epigenetic patterns of heritable gene expression that affect development, cellular plasticity, and tumor progression. In particular, the histone methyltransferase EZH2 is an important PcG component of the mammalian Polycomb repressive complex 2 (PRC2), which promotes gene silencing. EZH2 is linked to aggressive hepatocellular carcinoma (HCC) and has biomarker potential; however, the molecular details downstream of EZH2 and other PcGs are poorly defined. Gao and colleagues used gene profiling and chromatin immunoprecipitation (ChIP) to reveal that PcGs control critical gene networks. Interestingly, some networks had repressive H3K27me3 marks, while others, such as p53, did not, suggesting H3K27me3-independent mechanisms in HCC.

FGFR1 Is a Growth Driver in Malignant Pleural Mesothelioma

Marek *et al.* _____ Page 1460

Targeted therapeutics have not yet shown a significant impact on malignant pleural mesothelioma (MPM). Using both pharmacologic and molecular approaches, Marek and colleagues identified the tyrosine kinase FGFR1 as a nonmutated growth driver in a subset of MPM cells. Notably, FGFR1 expression was not associated with increased gene copy number (GCN) in multiple cell lines or primary MPM. The results of this study support FGFR1 expression as a biomarker of MPM sensitivity to FGFR-specific tyrosine kinase inhibitors rather than increased GCN, often used in clinical trials for this class of drugs. The findings also indicate that additional oncogenic events in MPM remain to be defined.

PTEN/PI3K Regulates the HIF α -VEGF Axis in Macrophages

Joshi *et al.* _____ Page 1520

The signaling pathways operational in macrophages regulating hypoxia-induced HIF α stabilization are a subject of intense investigation. Joshi and colleagues discovered that the PTEN/PI3K/AKT axis controls the degradation of HIF1 α and HIF2 α in macrophages under hypoxic conditions. Blocking PI3K/AKT signaling genetically or by a pan-PI3K inhibitor (SF1126) promoted the hypoxic degradation of HIF α via a 26S proteasome mechanism. Specifically, a macrophage-dominant PI3K isoform (p110 γ) was shown to control tumor growth, angiogenesis, metastasis, and the HIF α -VEGF axis. These findings indicate that PI3K inhibitors induce the hypoxic degradation of HIF and provide evidence that these inhibitors are excellent candidates for the treatment of cancers in which M2 macrophages promote tumor progression.