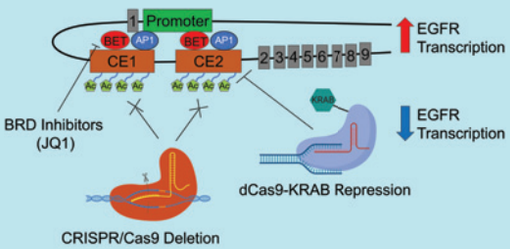
Molecular Cancer Research

Highlights

November 2019 • Volume 17 • Number 11

Selected Articles from This Issue



Intron 1–Mediated Regulation of *EGFR* Expression

Jameson *et al.* Page 2208

Signaling via epidermal growth factor receptor (EGFR) exerts a potent proliferative stimulus in cancer cells, but EGFR-targeted kinase inhibitors are readily overcome by a number of drug resistance mechanisms that have rendered sustained clinical benefit elusive. Here, Jameson and colleagues identify novel intragenic enhancers of *EGFR* expression in both glioblastoma (GBM) and head and neck squamous cell carcinoma (HNSCC) which are activated by the transcription factor AP-1 and bromodomain and extra-terminal (BET) epigenetic readers. Genetic disruption of enhancer sequences via CRISPR/Cas9 or suppression of enhancer activity with CRISPRi resulted in marked reduction of *EGFR* expression, and pharmacologic inhibition of AP-1 signaling or BET activity showed efficacy in suppressing both *EGFR* expression and proliferation in GBM and HNSCC cells. Overall, the study provides novel insight into the biology underlying *EGFR* expression in EGFR-driven cancers and provides a rationale for targeting epigenetic regulators as a means of sustained *EGFR* suppression in GBM and HNSCC.

mTOR Gene Promoter Haplotypes in Breast Cancer

Chen *et al.* Page 2244

Two discrete single nucleotide polymorphisms (SNP) in the mammalian target of rapamycin (*mTOR*) promoter have been documented to form a risk allele for breast cancer, but the biology underlying this observation is poorly understood. In this study, Chen and colleagues perform molecular profiling of the rs2295079 and rs2295080 SNPs to determine their role in disease progression. They find that rs2295079, which constitutes a C▶G transversion at position -78 relative to the *mTOR* transcriptional start site, forms a *de novo* KLF5 binding motif in the *mTOR* promoter. Similarly, the rs2295080 SNP at position -141 consists of a G▶T transversion which constitutes an emergent ZEB1 binding site. Finally, the authors show that the -78G/-141T haplotype promotes breast cancer aggressiveness through upregulation of mTOR, which subsequently drives enhanced proliferation via cyclin D1 expression as well as resistance to paclitaxel via upregulation of the ABCB1 efflux pump.

Anti-apoptotic Genes in Ovarian Cancer Drug Resistance

Stover *et al.* Page 2281

Resistance to platinum- and taxane-based chemotherapy occurs frequently in high-grade serous ovarian cancer (HGSOC), undermining long-term disease management and patient outcomes. Here, Stover and colleagues performed functional genomics screens to identify critical mediators of resistance to standard-of-care interventions in HGSOC cells. Among the candidate genes, BCL-2 family anti-apoptotic regulators were consistently identified in both gain- and loss-of-function screens and were shown to be commonly upregulated in HGSOC cells. Forced expression of BCL-2 family anti-apoptotic proteins were shown to be sufficient to induce platinum and taxane resistance *in vitro*, and pharmacological inhibition of BCL-XL and MCL1 sensitized ovarian cancer cells to treatment with platinum/taxane chemotherapy and the PARP inhibitor olaparib. Taken together, the data demonstrate a potential role for targeting the intrinsic apoptotic pathway as a means of enhancing the efficacy of clinically approved therapeutic modalities for HGSOC patients.

The HIF-Responsive Gene *GAL3ST1* Promotes Immune Cell Evasion

Robinson *et al.* Page 2306

Hyperactivated hypoxia inducible factor (HIF) signaling is a major driver of clear cell renal cell carcinoma (ccRCC) development and progression, largely resulting from loss of the Von Hippel-Lindau tumor suppressor, which negatively regulates HIF signaling. Here, Robinson and colleagues identify GAL3ST1, an enzyme responsible for the sulfonation of sulfolipids in the plasma membrane, as a key target of HIF signaling in ccRCC cells. Loss of GAL3ST1 expression resulted in reduced cell-surface sulfolipid expression, which in turn impaired the ability of tumor cells to bind to platelets when cultured concurrently *in vitro*. Notably, loss of tumor cell-platelet binding enhanced natural killer cell-mediated cytotoxicity versus ccRCC cells, suggesting that GAL3ST1 and sulfatide expression are key determinants of ccRCC immune evasion.

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Mol Cancer Res 2019;17:2143.