Molecular Cancer Research

Highlights

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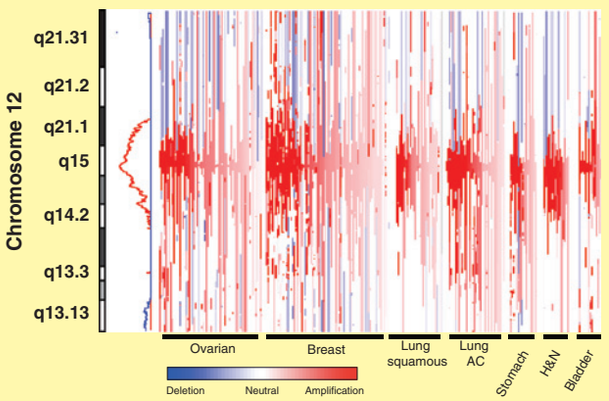
Selected Articles from This Issue



FRS2 Is an Ovarian Cancer Oncogene

Luo *et al.* Page 502

High-grade serous ovarian cancer (HGSOC) remains one of the most lethal cancer types despite aggressive standard treatment. HGSOC is characterized by widespread recurrent regions of copy number gain and loss. Luo and colleagues performed genomic analyses and interrogated a diverse number of genes that are recurrently amplified in HGSOC and are essential for cancer proliferation and survival in ovarian cancer cell lines. One of the genes, FGF receptor substrate 2 (*FRS2*), encodes an adaptor protein and induces transformation in immortalized human cell lines. These results implicate *FRS2* as an oncogene and a potential therapeutic target in a subset of HGSOC that harbors *FRS2* amplifications.

Polα and Human Telomeres

Diotti *et al.* Page 402

Telomere maintenance is essential for oncogenic transformation of human cells through the bypass of senescence, known to be an important tumor-suppressive mechanism. In addition to the three activities known to regulate telomere function (telomerase, shelterin, and the CST complex), a fourth complex was found to interact with these, the POLA/primase complex. Diotti and colleagues demonstrate that the polymerase-α (p180) enzyme and its regulatory subunit (p68) interact with telomeric complexes and are important for telomere function. Therefore specific DNA replication components play a role at telomeres and can be seen as relevant targets against tumor cell growth.

NHEJ Is a Target in High-Risk Neuroblastoma

Newman *et al.* Page 470

Neuroblastoma is a common solid tumor in children, and high-risk patients often present with genomic alterations suggesting the importance of DNA repair fidelity. Therefore, it is critical to identify components of the alternative NHEJ pathway as promising new therapeutic targets. Newman and colleagues identify a potential mechanistic explanation for the frequent chromosomal rearrangements found in neuroblastoma tumors. Importantly, clinical tumor specimens with high mRNA expression of alternative NHEJ pathway components have worse survival outcomes than those with low expression. These findings are of interest to both basic scientists in the DNA repair community and to clinical oncologists.

HIF1α in Prostate Cancer Stem Cells

Marhold *et al.* Page 556

HIF1α is a master regulator of adaptive responses to hypoxia, and its activation leads to metabolic reprogramming, angiogenesis, and tumor progression. Its role in hypoxic signaling in cancer stem cells (CSC) is not well known. Marhold and colleagues show that elevated HIF1α in a prostate CSC subpopulation leads to deregulated PI3K/AKT/mTOR. This suggests that CSCs rely on HIF1α-mediated inhibition of mTOR, which promotes CSC quiescence and survival in the hypoxic tumor microenvironment. Downregulation of HIF1α consequently attenuates this effect and increases proliferation of CSCs. This study also implicates primary resistance of CSCs to selective mTOR inhibition and provides a rationale for the use of dual PI3K/mTOR inhibitors.

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