Molecular Cancer Research

Highlights

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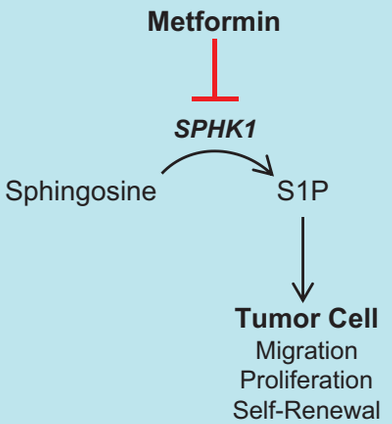
Selected Articles from This Issue



Metformin Targets SPHK1 in Ovarian Cancer

Hart *et al.* Page 870

The antidiabetic drug metformin has been shown to have anti-cancer properties that are poorly understood. Here, Hart and colleagues demonstrate that metformin inhibits the nuclear translocation and transcriptional activity of hypoxia-inducible factor (HIF)-1α and -2α. This in turn blocked the expression of sphingosine kinase 1 (SPHK1) and its target, sphingosine-1-phosphate (S1P), which are upregulated in ovarian cancer patients and are predictive of tumor aggressiveness and poor outcome. The authors suggest that patients with high SPHK1-S1P pathway activity may demonstrate considerable benefit from treatment with metformin.

STK17A Maintains Epithelial States in Colorectal Cancer

Short *et al.* Page 882

The epithelial-to-mesenchymal transition (EMT) is a critical step in the pathology and progression of cancer. In this study, Short and colleagues identify serine threonine kinase 17A (STK17A) as a key regulator of EMT in colorectal cancer. Loss of STK17A was associated with acquisition of a mesenchymal phenotype and increased invasive spread, whereas reactivation of STK17A signaling caused reversion to an epithelial phenotype and increased sensitivity to apoptotic signaling. Taken together, their data indicate a novel role for STK17A in controlling metastatic spread in colorectal cancer.

Cisplatin Shapes Osteosarcoma Clonal Evolution

Brady *et al.* Page 895

Cisplatin therapy is a key component of the standard of care for pediatric osteosarcoma, but its potential to increase mutational burden in the tumor has yet to be defined. Here, Brady and colleagues demonstrate a unique mutational signature in metastatic samples from patients treated with cisplatin. The cisplatin signature accounted for greater than 40% of mutations in metastatic lesions and was associated with acquisition of putative driver mutations upon seeding of distant metastases. These data indicate widespread clonal heterogeneity in metastatic osteosarcoma, which could inform the optimal treatment of patients with recurrent disease.

Radiation-Induced Malignant Transformation

Repullés *et al.* Page 937

Ionizing radiation (IR) is a common treatment modality for many localized cancers, but its widespread genotoxic effects have the potential to induce tumorigenic mutations as well. Repullés and colleagues demonstrate that IR delivered to primary breast cells resulted in increased colony size and disrupted cellular polarity. Additionally, immortalized pre-malignant cells bearing hTERT and SV40 small and large T antigens displayed heightened sensitivity to radiation-induced cell transformation. Though cells from different donors displayed differential sensitivity to IR, these data imply that patients bearing premalignant genetic lesions may be at increased risk of developing oncogenic driver mutations in response to radiotherapy.