Molecular Cancer Therapeutics

Highlights

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Selected Articles from This Issue

hTERT Promotes Imatinib Resistance in CML

Deville *et al.* **Page 711**

Despite satisfactory remission rates, resistance to imatinib is an important issue for therapy of chronic myeloid leukemia. Deville and colleagues showed that the emergence of resistance occurred faster in cells overexpressing the catalytic subunit of the telomerase, showing that this enzyme represents an additional factor in the development of imatinib resistance. Furthermore, strategies targeting either telomerase expression or activity restored imatinib sensitivity in the resistant cells. Therefore, combining antitelomerase strategies to imatinib treatment represents an attractive approach to prevent the emergence of imatinib-resistant clones and increase the probability to eradicate the disease.

PP2A: A Novel Therapeutic Target in Prostate Cancer

Bhardwaj *et al.* **Page 720**

PP2A is a major serine/threonine phosphatase and a potent tumor suppressor; however, its role in prostate cancer has remained underexplored. Bhardwaj and colleagues have now shown that PP2A activity is inversely associated with androgen-independent growth of prostate cancer cells. Their data reveal a novel mechanism, whereby loss of PP2A-mediated checkpoints leads to the activation of Akt and ERK and partially sustains androgen-receptor signaling under steroid-deprived condition. Their findings offer potential therapeutic implications for targeting PP2A in castration-resistant prostate cancer.

Chemical Modulation of the Mitotic Checkpoint

Riffell *et al.* **Page 839**

Exposure of cells to microtubule-targeting cancer drugs such as paclitaxel causes mitotic arrest by activation of the mitotic checkpoint. Some cells can escape mitotic arrest by entering interphase without dividing, a process termed mitotic slippage. Riffell and colleagues examine mechanisms underlying mitotic slippage using two chemicals found to induce slippage. SU6656 and geraldol induced mitotic slippage through caspase-3-dependent degradation of the checkpoint kinase BubR1, thus permitting proteasome-dependent degradation of cyclin B1 and escape from drug-induced mitotic arrest. The identification of this pathway linking apoptosis with mitotic control may have implications for cancer therapy.

Monitoring Drug Efficacy in Hepatocellular Carcinoma

van Zijl *et al.* **Page 850**

The epithelial to mesenchymal transition (EMT) of malignant hepatocytes is a crucial event in hepatocellular carcinoma (HCC) progression and recurrence. In this study, van Zijl and colleagues established a novel and unique cellular EMT model of human HCC to identify molecular mechanisms and to assess therapeutic drug efficacy during liver carcinoma progression. Most remarkably, they found that the combined treatment with doxorubicin and sorafenib caused increased susceptibility of HCC cell types before and after EMT, resulting in enhanced drug efficacy. This model of EMT that reliably reflects human HCC progression is an invaluable tool in preclinical studies for the identification of molecular mechanisms underlying HCC progression, the pharmacological determination of dose-effect relationships and thus the efficacy of single and combined treatments with novel and currently used anti-cancer drugs, and the (re)-evaluation of drug target specificity and pleiotropic effects.