Clinical Cancer Research

Highlights

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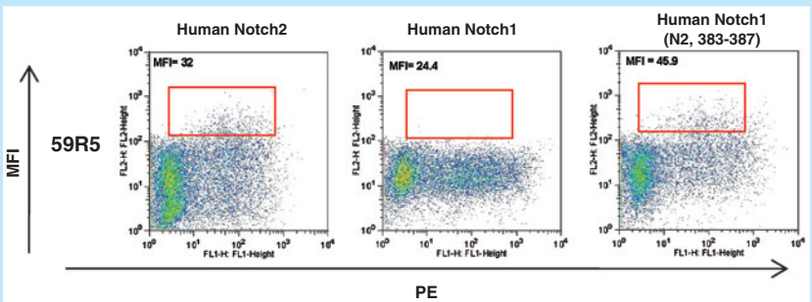
Selected Articles from This Issue



Antitumor Effect of Notch2/3 Antagonist (Tarextumab)

Yen *et al.* Page 2084

Dysregulation of Notch signaling promotes cancer growth through several mechanisms, including the maintenance of tumorigenic cells and functional tumor vasculature. Yen and colleagues report the development and characterization of a dual antagonist antibody that inhibits both Notch2 and Notch3 (OMP-59R5, tarextumab). OMP-59R5 inhibited tumor growth, decreased cancer stem cell frequency, and modulated the function of tumor vasculature in a variety of patient-derived xenografts. In pancreatic cancer, efficacy was associated with higher levels of Notch3 expression, providing a potential biomarker for patient selection. Tarextumab is currently advancing in Phase 2 clinical testing for treatment of pancreatic and small cell lung cancers.

MIR27A Polymorphisms and Fluoropyrimidine Toxicity

Amstutz *et al.* Page 2038

The microRNA miR-27a directly regulates dihydropyrimidine dehydrogenase (DPD), the key enzyme in fluoropyrimidine catabolism. To investigate if miR-27a may influence toxicity risk in fluoropyrimidine-based chemotherapy, Amstutz and colleagues assessed the association of genetic polymorphisms in *MIR27A* with early-onset fluoropyrimidine toxicity. The common *MIR27A* variant rs895819—previously shown to affect miR-27a levels—was strongly associated with severe early-onset toxicity in patients also carrying risk variants in the DPD gene. This suggests that miR-27a and polymorphisms affecting its expression may serve as novel, complementary markers for further patient risk stratification in DPD risk variant carriers to improve the specificity of genetic testing.

Chemotherapy Contributes to Drug Resistance

Saggar *et al.* Page 2107

Chemotherapy targets rapidly proliferating cells, thus sparing slowly-dividing hypoxic cells that can contribute to repopulation in between courses of treatment. Hypoxia-activated prodrugs (TH-302) selectively kill hypoxic cells and may inhibit tumor repopulation and, in combination with chemotherapy, may increase tumor control. Saggar and colleagues investigated changes in reoxygenation within the tumor microenvironment by administrating two sequential markers of hypoxia following treatment with doxorubicin/docetaxel +/− TH-302. It was found that (i) chemotherapy induces reoxygenation of previously hypoxic cells and leads to tumour repopulation, and (ii) TH-302 reduces this effect. This supports the potential of TH-302 to increase therapeutic effects of chemotherapy.

EGFR Mutations and Resistance to Cetuximab

Arena *et al.* Page 2157

EGFR blockade with the antibody cetuximab is effective in patients with wt-RAS metastatic colorectal cancer (CRC). Unfortunately, responses are transient and patients invariably develop acquired resistance. Arena and colleagues analyzed the genetic profile of clinical samples and preclinical models of acquired resistance to cetuximab. They identified five novel point mutations in the EGFR ectodomain, which confer resistance to cetuximab in CRC patients and cells. Functional analysis of cellular models revealed that a subset of the EGFR mutations retains sensitivity to panitumumab. This knowledge is being incorporated in clinical trials aimed at overcoming acquired resistance to cetuximab in colorectal cancer patients.

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