Cancer Research

Highlights

Selected Articles from This Issue

March 15, 2009

Germ-Line CNV at 2p24.3 and Prostate Cancer Risk

Liu *et al.* _____ **Page 2176**

Although copy number variations (CNVs) are common in the human genome, their associations with risk of common diseases are not well understood. To explore the relationship between CNVs and the risk of prostate cancer, Liu and colleagues performed a two-stage genome-wide association study using three populations from Sweden and the United States. Among 4,314 cases and 2,176 controls, the authors found that the CNV at 2p24.3 was significantly associated with prostate cancer risk. More importantly, the association was stronger for aggressive prostate cancer than for nonaggressive prostate cancer. While the biological effect of this germ-line CNV is unknown, this result is important because it represents the first novel germ-line CNV identified via a genome-wide search for association with prostate cancer risk.

Engineered Knottin Peptides as *In vivo* Imaging Agents

Kimura *et al.* _____ **Page 2435**

Integrins are attractive targets for cancer therapeutic intervention and, thus, molecular imaging agents are needed to identify patients who will best respond to these targeted therapies and to monitor disease progression. Kimura and colleagues recently engineered small (~3 kDa), conformationally constrained knottin peptides that bind to $\alpha_v\beta_3/\alpha_v\beta_5$ or $\alpha_v\beta_3/\alpha_v\beta_5/\alpha_5\beta_1$ integrins with low nmol/L affinity and evaluated their potential as *in vivo* imaging agents for optical and positron emission tomography imaging. The authors show that high-affinity integrin-binding knottin peptides exhibit significantly increased tumor uptake in mice compared with weaker binding peptides. These results, coupled with low nonspecific uptake in organs such as the liver, indicate that engineered knottin peptides have potential as clinical diagnostics for a variety of cancers.

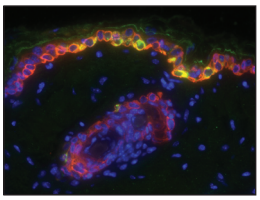
Natural Killer Cells and Selectins in Tumor Suppression

Sobolev *et al.* _____ **Page 2531**

Natural killer (NK) cells play an important role in killing cancer cells *in vitro* and are believed to play diverse roles in suppression of cancer growth *in vivo*. While the mechanisms by which NK cells recognize and destroy cancer cells are becoming reasonably well established, how NK cells reach their sites of action *in vivo* is not well understood. Sobolev and colleagues demonstrate that selectins, a family of cell adhesion molecules important in leukocyte recruitment to sites of inflammation and infection, are necessary for NK cells to infiltrate and kill subcutaneous tumors. This study reveals a role for selectins in NK cell recruitment to tumors and in the regulation of tumor immunity.

HIF-1α and Carcinogenic Suppression

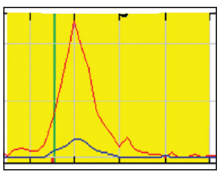
Scortegagna *et al.* _____ **Page 2638**



HIF-1α is up-regulated in solid malignancies, functioning as a facilitator of tumor growth, invasion, and metastasis. However, the role of HIF-1 during multistage carcinogenesis is unknown. Scortegagna and colleagues tested HIF-1 gain of function during multistage murine skin chemical carcinogenesis in K14-HIF-1αDPM transgenic mice. The authors report that while papillomagenesis was facilitated, malignant conversion was inhibited and that inhibition was associated with up-regulation of the tumor suppressor *NDRG1*. Moreover, *SELENBP1*, previously identified as being lost in a spectrum of epithelial cancers, was discovered to be a novel HIF-1α target gene. These results suggest that different drug targeting of HIF-1 function may be required in cancer prevention compared with therapy of established malignancies.

Rapamycin Activates AKT through CDC25B

Chen *et al.* _____ **Page 2663**



The anticancer effect of mTOR inhibitors, rapamycin and its derivatives, in the clinic has been limited and could be explained by recent observations of rapamycin-dependent induction of oncogenic cascades. Chen and colleagues investigated rapamycin-dependent phosphoproteomics and identified 250 phosphosites in 161 cellular proteins that are sensitive to rapamycin. A siRNA-dependent screening showed that AKT induction by rapamycin was attenuated by depletion of cellular CDC25B. Additional experiments demonstrated that CDC25B transduces rapamycin-induced oncogenic AKT activity. These data advance the global mechanistic understanding of rapamycin's action in cancer and also suggest that CDC25B may serve as a drug target for improving mTOR-targeted cancer therapies.

Intratumoral Immune Reaction in Human Colorectal Cancer

Camus *et al.* _____ **Page 2685**

The impact of immune responses and tumor escape on patient prognosis is still poorly understood. Camus and colleagues investigated *in situ* immune responses in human colorectal cancer (CRC), according to metastatic lymph node or distant organ invasion (META– or META+ patients). META– patients presented significant correlations between cytotoxicity and effector memory T-cell subpopulations. These correlation profiles were absent in tumors with low T-cell infiltrates and were altered in META+ patients with high T-cell infiltrates. Overall investigation of the CRC primary tumor microenvironment uncovered four major intratumoral immune profiles. These results highlight optimal and altered immune correlation profiles to define patient outcome.