Molecular Cancer Research

Highlights

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Selected Articles from This Issue

Epithelia-stroma Crosstalk in Right Colon ACF

Mo *et al.* Page 795

The development of an ultra-sensitive laser capture microdissection (LCM)/RNA-seq approach for studying epithelial and stromal compartments of human aberrant crypt foci (ACF) is described that focuses on proximal colon lesions harboring somatic mutations to KRAS, BRAF or APC. Pro-inflammatory NF-kB target genes (TIMP1, RELA and RELB) were identified as specific to ACF epithelia. A subset of BRAF-mutant ACF displayed a senescence-associated transcriptome with increased expression of CDKN2A. LCM-captured ACF-associated stroma are transcriptionally distinct from normal, with up-regulation of genes related to immune cell infiltration and fibroblast activation. These findings underscore the dynamic, complex interplay occurring early in colorectal neoplasia, highlighting the role of activated stromal fibroblasts and potential therapeutic targeting of NF-kB signaling for cancer prevention.

DNA Methylome of Ovarian Cancer and Tissues of Origin

Klinkebiel *et al.* Page 787

High-grade serous ovarian cancer (HGSC) is the most common and lethal ovarian cancer. Two tissues have been suggested as its origin: ovarian surface and fallopian tube epithelia (OSE and FTE). Klinkebiel and colleagues hypothesized that the HGSC methylome will more closely resemble the methylome of its tissue of origin. DNA methylome profiling of patient-matched primary normal OSE and FTE, as well as primary HGSC obtained from various sources was performed. The data support the FTE origin model and suggest that DNA methylome profiling is a valuable approach to examine cell lineage in cancer, due to its tissue-specificity and biochemical stability.

PADI2 is Lost in CRC

Cantariño *et al.* Page 841

The pathological role of the enzyme peptidyl arginine deiminase 2 (PADI2) has been studied in autoimmune diseases and, very recently, in breast and skin cancer. Here, down-regulation of PADI2 is an early event in the pathogenesis of colorectal cancer associated with poor prognosis. PADI2 mRNA and protein levels, in independent cohorts, were found to be low or absent in tumors as well as in ulcerative colitis and cell line samples. PADI2 up-regulation was detected in matched normal mucosa and in differentiated cells *in vitro*. Moreover, low levels of PADI2 in both tumors and adjacent mucosa correlate with decreased patient survival independently of inflammation. These data suggest that PADI2 is a potential biomarker or a point for therapeutic intervention.

Wnt Pathway Inhibition by an LRP6 Bi-Specific dAb

Jackson *et al.* Page 859

Low density lipoprotein (LDL) related protein 6 (LRP6), is an important receptor component of the WNT pathway, often dysregulated during tumorigenesis, and is therefore an attractive target for inhibitory antibodies. However, LRP6 is unusual in that it has two spatially distinct ligand binding sites. Monospecific antibodies are unable to block both sites, and often potentiate signaling instead of blocking it. Using domain antibody technology, Jackson and colleagues constructed a bispecific molecule that fully inhibits this complex receptor molecule. Importantly, this bi-specific antibody is active both *in vitro* using cancer cells and *in vivo* using patient-derived tumor models.

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