Molecular Cancer Research

Highlights

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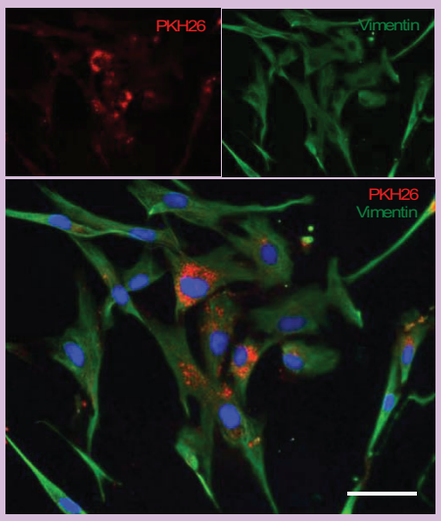
Selected Articles from This Issue



Cancer Exosomes Induce Fibroblast Differentiation into CAFs

Goulet *et al.* Page 1196

Cancer-associated fibroblasts (CAFs) promote cancer growth and metastasis. However, mechanistic understanding by which cancer cells promote activation of healthy fibroblasts into CAFs remains elusive. In the current issue, Goulet and colleagues demonstrate that exosomes released by bladder cancer cells are internalized by healthy fibroblasts (HFs) to promote CAF differentiation through the activation of the TGFβ/SMAD signaling pathway. In fact, exosomal TGFβ, shown to be localized inside the vesicle, contributed 53 to 86% of the total TGFβ present in the bladder cancer cell conditioned medium. In conclusion, this study highlights that TGFβ-derived cancer exosomes are important molecular modulators of tumor microenvironment and CAF differentiation.

IR-induced PARPi Cytotoxicity Depends on p53

Sizemore *et al.* Page 1092

PARP inhibitors (PARPi) are synthetically lethal in tumors carrying BRCA1/2 mutations and with deficiencies in homologous recombination (HR)-mediated DNA repair. However, BRCA mutations are rare; thus, most tumors are resistant to PARPi. Sizemore and colleagues demonstrate that ionizing radiation (IR) induces BRCA1 sequestration to the cytoplasm and DNA repair deficiency, and subsequent PARPi synthetic lethality in multiple tumor model systems. Importantly, p53 status was discovered to be a significant determining factor of tumor cell sensitization to PARPi following IR. These results have the potential to significantly increase the number of patients who may clinically benefit from PARPi-based therapies.

Noncoding Mutations on RNA Binding Protein Motifs in Cancer

Singh *et al.* Page 1112

Cancer genomics has highlighted the prevalence of sequence variants of unknown significance. Singh and colleagues hypothesized that a fraction of these mutations reflect RNA-related selection processes, thereby impacting RNA metabolism and contributing to oncogenic processes. Analysis of whole-genome sequencing (WGS) data from multiple cancers uncovered frequent mutations in binding sites for RNA binding proteins and splicing regulators. Furthermore, RNA sequencing (RNA-seq) data from the same specimens validated a change in RNA processing in association to these mutations. The study describes new alterations in cancer that impact RNA processing and proposes a systematic method for the interpretation of non-coding variants in cancer genomes.

Role of USP22 in Lung Adenocarcinoma CICs

Yun *et al.* Page 1161

Histone 2B monoubiquitination (H2Bub1) is commonly lost during carcinogenesis and is deubiquitinated by ubiquitin-specific peptidase 22 (USP22). Here, the impact of USP22 on stem cell characteristics and cisplatin resistance was investigated in cancer-initiating cells (CICs) derived from human lung adenocarcinomas. Elevated USP22 expression associated with stem-like characteristics and chemotherapy resistance. Furthermore, ALDH1A3 which has been implicated in cisplatin resistance in lung adenocarcinoma was down-regulated upon USP22 knockdown. These data demonstrate that USP22 plays a critical role in tumorgenicity and cisplatin resistance in lung adenocarcinoma and may be a useful target for therapy.

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