Molecular Cancer Research

Highlights

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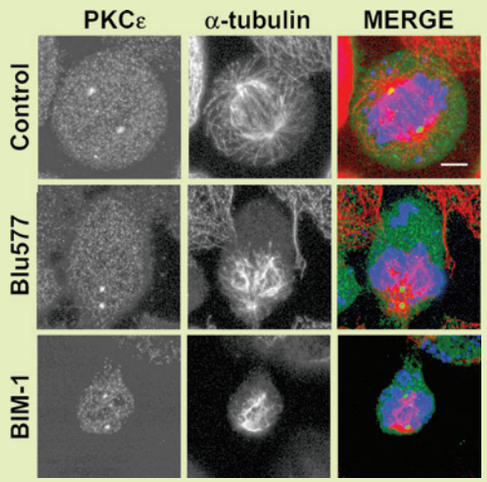
Selected Articles from This Issue



Early Mitotic Progression is Regulated by PKCε

Martini *et al.* Page 3

Protein Kinase C-epsilon (PKCε) has recently emerged as a key regulator of several cell-cycle processes associated with DNA stress. Here, Martini and colleagues demonstrate the engagement of PKCε in the modulation of prophase-to-metaphase progression. Live imaging and immunofluorescence analyses reveal that the inhibition of PKCε results in a delay of centrosome migration and mitotic spindle organization. The close relationship between PKCε dependency for mitotic spindle organization and the impairment of the TOPO2A-dependent G_2 cell cycle arrest, a hallmark of transformed cells, strongly indicated PKCε as a target in cancer therapy.

MNK1 Regulates ATO Responses in GSCs

Bell *et al.* Page 32

Glioblastoma multiforme (GBM) is a highly aggressive cancer in the brain. Despite recent success using temozolomide, recurrence is common and survival rates remain poor. Therefore, additional treatment options are needed. One option is to target GBM subtypes or cell populations that may increase resistance or recurrence. To this end, patient-derived xenografts (PDXs) were screened with a small-molecule library to identify compounds with differential activity against GBM subtypes. Arsenic trioxide (ATO) was validated as a potent subtype-specific compound that activated the MNK1-eIF4E signaling axis. Examination of phase I/II clinical data of patients on ATO revealed subtype-specific clinical response. Subtype-specific resistance to ATO was mediated by activation of the MNK1-eIF4E signaling axis. Thus, targeting MNK1 may provide therapeutic benefit in response to ATO treatment of GBM.

EP300 and CREBBP Mutations in Bladder Cancer

Duex *et al.* Page 69

The chromatin remodeling gene EP300 and its paralog CREBBP are mutated in a third of bladder cancer patients. Knowing which tumor mutations are functionally relevant is critical, but determining this experimentally is time and cost intensive. Duex and colleagues determined which mutations had functional impact and investigated the correlation between this and bioinformatic prediction. Interestingly, the results of the prediction software correlated 100% with those of functional assessment. A gene signature reporting on bioinformatically predicted inactivating mutations correlated with advanced bladder cancer. This study highlights the potential of bioinformatics to leverage limited functional analysis to inform on patient outcomes and potential therapeutics.

Novel Regulators of TGFα Shedding

Wilson *et al.* Page 147

Pathways and mechanisms underlying dysregulation of growth factor shedding, which is involved in many pathologies including kidney disease and cancer, are at present poorly understood. Toward addressing this problem, a combined experimental and computational approach was pursued to uncover genetic mediators of the dysregulated tumor growth factor-alpha (TGFα). Wilson and colleagues used a foundational shRNA screen to identify genetic mediators of TGFα shedding, uncovered hidden information from this screen using a computational network approach, and validated these newly predicted regulators for their effects on shedding. Combined, this study highlights the utility of this integrative approach for novel therapeutic discovery.

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