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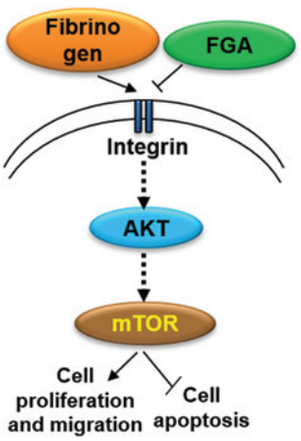
MOLECULAR CANCER RESEARCH

HIGHLIGHTS

Selected Articles from This Issue

Role of FGA in Lung Cancer



Wang *et al.* | Page 943

Interactions between tumor cells and the extracellular matrix (ECM) provide both pro- and anti-tumorigenic stimuli and guide the development of cancer. Fibrinogen-α (FGA)—a subunit of the ECM protein Fibrinogen—has recently come under scrutiny as a key anti-tumorigenic factor, but the underlying mechanism is not yet understood. Here, Wang and colleagues employ CRISPR/Cas9 genome editing to ablate FGA from lung cancer cell lines, showing subsequent enhancement of cell migration and colony formation, with a corresponding increase in mesenchymal features. Mechanistically, the authors demonstrate that FGA interacts with integrin α5, and that this interaction is critical to control AKT-mTOR signaling in lung cancer cells. Supplementation of FGA into the growth medium, or co-culturing FGA-knockout cells with FGA-replete cells, resulted in restoration of the fibrinogen-integrin signaling pathway in FGA-knockout cells and suppression of cell growth and migration. Overall, the data support a key role for FGA in controlling tumor progression in the lung.

BMP4 Inhibition of GBM Proliferation via Suppression of SOX2

Dalmo *et al.* | Page 981

Glioblastoma multiforme (GBM) is a highly aggressive brain cancer with limited treatment options stemming from a high degree of molecular heterogeneity. Recently, controversy over the role of bone morphogenic protein 4 (BMP4) has arisen, with some reports suggesting that it may be a potent antiproliferative agent and others reporting no strong effect. Now, new data from Dalmo and colleagues suggests that SOX2 may be a determining factor in GBM responses to BMP4. While responses to BMP4 were varied, transcriptome sequencing of a panel of human GBM-initiating cultures identified a SOX2-responsive gene expression program in cultures that responded to BMP4. In the responsive subset, BMP4 signaling through SMAD 1/5/9 caused repression of SOX2 expression, whereas forced expression of SOX2 negated the effect of BMP4 in these cells. Taken together, the data suggest a mechanistic basis for the heterogeneous response to BMP4 in GBM cultures and identify a subset of GBM cases in which BMP4-based therapy could be effective.

NF-kB Promotes Tamoxifen Tolerance and Tumor Recurrence

Kastrati *et al.* | Page 1018

Tamoxifen therapy is a cornerstone of the clinical standard-of-care for estrogen receptor-positive breast cancers, and resistance to tamoxifen contributes to disease progression and poor outcomes. Thus, mechanistic data are urgently needed to address resistance mechanisms. In this study, Kastrati and colleagues identify NF-κB signaling as a key determinant of the progression to tamoxifen resistance. Pathway analysis of comparative transcriptomics from tamoxifen-treated versus -untreated patients with breast tumors identified an NF-κB-dependent gene signature, which was confirmed in cell lines and xenograft tumors. Moreover, both ablation of NF-κB expression using CRISPR/Cas9 and inhibition of the pathway demonstrated that NF-κB was necessary for cell survival in the presence of tamoxifen *in vitro* as well as for tumor recurrence following tamoxifen therapy *in vivo*. The authors conclude that NF-κB-directed therapy may extend the efficacy of tamoxifen in the clinic and delay the onset of recurrent disease.

AE 51310 Suppresses Oncogenic Signaling in Lung Cancer

Wang *et al.* | Page 1028

G-protein-coupled receptors (GPCR) are a diverse family of cell surface receptors whose activity and tissue distribution are varied across tissues and are frequently deregulated and co-opted to promote tumorigenesis. One such GPCR, opsin4/melanopsin (OPN4), is typically expressed in the brain and regulates circadian rhythms and sleep patterns. Here, Wang and colleagues demonstrate that OPN4 is commonly overexpressed in non-small cell lung cancers (NSCLC) and is linked to poor prognosis. Mechanistically, OPN4 was found to signal through the large G protein subunit Gα11 and subsequently activate protein kinase C and the Raf/Mek/Erk cascade. Genetic ablation of *OPN4* significantly suppressed urethane-induced tumorigenesis *in vivo*, suggesting that it may harbor a central role in lung carcinogenesis. Moreover, the authors present the first evidence for AE 51310—an OPN4 inhibitor—which was shown to have significant suppressive effects on NSCLC growth both *in vitro* and *in vivo*.

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