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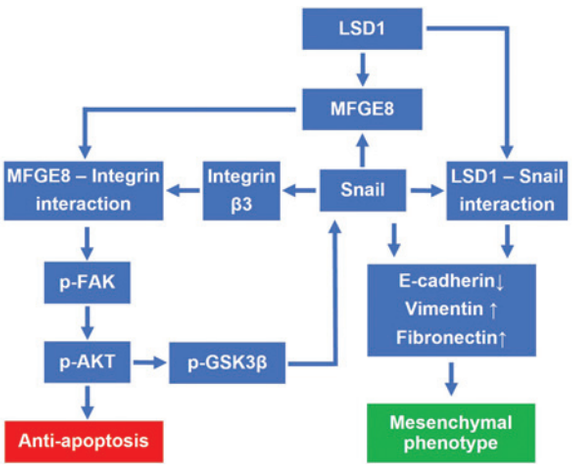
MOLECULAR CANCER RESEARCH

HIGHLIGHTS

Selected Articles from This Issue

Suppressing LSD1 to Target Mesenchymal Phenotype in MPM



Wirawan *et al.* | Page 127

Malignant pleural mesothelioma (MPM) is a highly aggressive cancer that lacks effective therapeutic options, owing to chemotherapeutic resistance and lack of currently targetable oncogenic mutations. However, mutations in histone modifiers documented in MPM represent exciting potential therapeutic targets. Wirawan and colleagues used estrogen receptor sensitive Snail variant mesenchymal and sarcomatoid-like MPM cell lines to show that lysine-specific demethylase 1 (LSD1) drives a MPM mesenchymal phenotype, tumor cell migration, and cisplatin resistance. The authors integrated microarray, phosphokinase array, and assay for transposase-accessible chromatin using sequencing (ATAC-seq) analyses to identify milk fat globulin protein E8 (MFGE8) as the LSD1-mediated driver of cisplatin resistance. Subsequent experiments demonstrated that MFGE8 interaction with integrin β3 drives FAK and AKT phosphorylation, initiating a positive feedback loop that upregulates Snail expression and promotes its associated mesenchymal phenotype. In sum, the work presented suggests that LSD1 may be a multifactorial therapeutic target for MPM.

AR/GLI3 Cross-Talk Drives Progression to CRPC

Burleson *et al.* | Page 62

While androgen deprivation can provide at least temporary benefit for men with metastatic prostate cancer, most patients go on to develop lethal castration-resistant prostate cancer (CRPC). Speckle-type POZ protein (SPOP) mutations and Sonic hedgehog (SHH)-mediated androgen receptor (AR) signaling activation are prevalent in CRPC, making each therapeutic targets of interest for the disease. In their study, Burleson and colleagues demonstrate that a transcriptional activator of the SHH pathway, GLI3, enhances SHH signaling and cell proliferation in androgen-deprived prostate cancer cells. The authors show that GLI3 is post-translationally stabilized by somatic SPOP mutations, and that stabilized GLI3 partners with AR to induce a gene expression program that promotes tumor cell proliferation *in vitro* and *in vivo*. CRPC patients whose tumors expressed the GLI3 gene signature displayed higher biochemical relapse rates, suggesting that the signature may identify patients at high risk of disease progression. Overall, the presented data provide a novel mechanistic link between SPOP mutations and SHH-mediated AR signaling activation that could inform prognostic and therapeutic strategies for CRPC moving forward.

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Antiangiogenic Properties of IQGAP2

Kumar *et al.* | Page 77

The efficacy of antiangiogenic cancer therapies has been limited by side effects and therapeutic resistance, suggesting that targeting angiogenesis alongside other oncogenic processes may be more effective than targeting angiogenesis alone. Recent work linking low IQ motif-containing GTPase-activating protein 2 (IQGAP2) expression to breast tumor epithelial–mesenchymal transition (EMT), angiogenesis, and poor patient outcomes makes IQGAP2 an intriguing therapeutic candidate. Kumar and colleagues used IQGAP2 ablation and overexpression in both estrogen receptor-positive and -negative breast cancer cell lines to demonstrate that IQGAP2 reduction in those cell lines increases endothelial cell proliferation and migration. Accordingly, IQGAP2 reduction increased vascular density in chick chorioallantoic membranes and wound healing assays, which supported the authors' observation that IQGAP2 expression inversely correlated with endothelial cell abundance in tumor cells from breast cancer patients. The authors mechanistically attributed their findings to increased ERK-VEGF-A signaling in tumor cells, which activated VEGFR2-AKT signaling in endothelial cells. Results from the study position IQGAP2 as a next-generation anti-angiogenic therapeutic target potentially capable of simultaneously inhibiting angiogenesis and EMT.

EBV Promotes LN Metastasis of NPC

Li *et al.* | Page 161

Draining lymph node metastasis is often noted upon nasopharyngeal carcinoma (NPC) diagnosis, and can mark an initial stage of progressive metastatic dissemination. While Epstein-Barr virus (EBV) has long been associated with NPC, its role in initial metastatic processes has not been defined. In their study, Li and colleagues used EBV-infected and functional EBV knockout NPC cell lines to demonstrate that EBV-positive NPC induces lymphatic endothelial cell proliferation and migration. Gene expression analysis revealed elevated VEGF-C expression in NPC infected with EBV, and the authors showed that VEGF-C was responsible for EBV-induced lymphangiogenesis. Further work demonstrated that EBV miRNA BART15 targets PHLPP1 in NPC cells, resulting in increased AKT phosphorylation, HIF-1α activation, and VEGF-C production. Moreover, patients with EBV-positive NPC displayed higher levels of lymphangiogenesis and lymph node metastasis. Taken together, the presented work sheds light on how EBV induces early NPC progression and elucidates a molecular pathway that could be therapeutically targeted.