



mTOR Inhibition Enhances the Efficacy of Aurora Inhibitors

Liu *et al.* _____ Page 1326

Aurora kinase overexpression is known to be important for tumor development and progression. Although Aurora kinase inhibitors have significant therapeutic potential, their single-agent efficacy appears to be uniformly modest and needs improvement. Liu and colleagues reveal that AML cells with polyploidy, induced by Aurora kinase inhibition, have elevated glycolytic metabolism and are sensitive to metabolic deprivation or glycolytic inhibitors like 2DG (2-deoxy-D-glucose). Moreover, mTOR inhibition suppressed the metabolism of polyploidy cells and promoted an autophagic response and apoptotic death. Notably, p62 (*SQSTM1*) was demonstrated to be a metabolic regulator in polyploidy cells. These findings indicate that mTOR inhibition enhances the efficiency of Aurora kinase inhibitors and provide a novel treatment strategy against AML.

miR-106a in Ovarian Serous Carcinoma

Liu *et al.* _____ Page 1314

High-grade serous ovarian cancers (HGSOC) are poorly differentiated and fast-growing tumors. The molecular mechanism for HGSOC differentiation remains unknown. microRNAs play an important role in early development and cell differentiation. Therefore, Liu and colleagues performed global microRNA profiling, which revealed that miR-106a is frequently upregulated in HGSOC. Importantly, miR-106a overexpression in normal and malignant cell lines resulted in increased cellular proliferation, expanded side populations, and increased tumor initial/stem cell populations both *in vitro* and *in vivo*. Furthermore, miR-106a-mediated tumor differentiation was largely contributed by repression of p130 (*RBL2*), an RB tumor suppressor family member. As such, downregulation of *RBL2* by miR-106a represents a major molecular event that may underwrite the aggressive and poorly differentiated nature of HGSOC.

Twist Box is Needed for Prostate Cancer Metastasis

Gajula *et al.* _____ Page 1387

Twist1 is a prime player during development and is a master transcriptional regulator of the epithelial-mesenchymal transition that promotes cancer metastasis. Gajula and colleagues demonstrate three relevant findings for prostate cancers that overexpress Twist1: First, Twist1 leads to elevated cytoskeletal stiffness and traction forces at the migratory edge of cell collections; Second, the Twist box domain is required for Twist1-induced prometastatic processes *in vitro* and metastases *in vivo*; and Third, Hoxa9 is a novel Twist1 transcriptional target that is required for Twist1-induced prometastatic phenotypes. Thus, targeting the Twist box domain and Hoxa9 may effectively limit prostate cancer metastatic potential.

LOXL2 Drives Fibroblast Activation

Barker *et al.* _____ Page 1425

Fibroblast interactions in the extracellular matrix are critical for normal tissue homeostasis. Cancer-associated fibroblasts are a heterogeneous population of cells that support malignant progression through multiple mechanisms. Barker and colleagues discovered that tumor-derived and secreted lysyl oxidase-like-2 (LOXL2) is vital for stromal fibroblast activation in orthotopically grown mammary tumors. A reduction in fibroblast-associated α -smooth muscle actin was demonstrated using genetic and antibody inhibitory approaches directed against LOXL2. Tumor-derived or recombinant LOXL2 promoted fibroblast properties necessary for metastasis. Importantly, it was shown that LOXL2 fibroblast activation was dependent on integrin-mediated focal adhesion kinase signaling. This novel function of LOXL2 highlights the potential for targeted approaches to prevent tumor progression.

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