Molecular Cancer Research

Highlights

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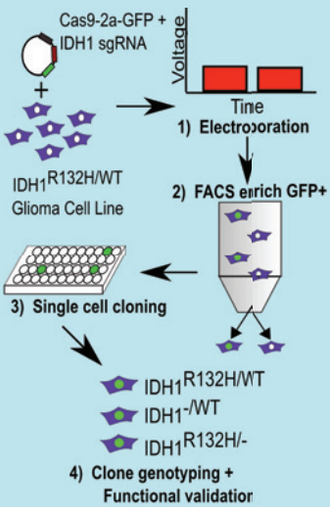
Selected Articles from This Issue



Modeling Loss of IDH1 R132H by CRISPR-Cas9

Moure *et al.* Page 2042

Mutations in the active site of isocitrate dehydrogenase (IDH) 1 and 2 are thought to cause the glioma CpG island methylation phenotype (G-CIMP) via production of D-2-hydroxyglutarate (D-2HG). The loss of the mutant allele occurs in advanced disease and is thought to impact tumor phenotypes including G-CIMP, but the biology underlying and resulting from these events is poorly understood. Using patient-derived glioma cells, Moure and colleagues show that loss of IDH1 mutant-mediated D-2HG production is not sufficient to remove many DNA methylation marks within the context of CpG islands, but may contribute to global changes in overall DNA methylation states, resulting in the development of a G-CIMP-low–like phenotype previously associated with worse outcomes. Further, this study establishes novel, genetically relevant models to further study the contribution of IDH1 mutations to glioma progression.

Loss of MAP3K7 Disrupts HR and Induces Cell Death

Washino *et al.* Page 1985

Genetic disruption of tumor suppressor expression is a major driver of tumorigenesis and disease progression, which currently cannot be targeted directly. Here, Washino and colleagues employ a systems pharmacology approach to identify altered signaling pathway activity in aggressive prostate cancers that had lost *MAP3K7* and *CDH1*. Computational analysis of signaling activity in TCGA datasets identified cyclin-dependent kinase (CDK) 1 and 2 signaling as key downstream effectors of the aggressive phenotype. CDK1/2 inhibition with dinaciclib had profound effects on cells with *MAP3K7* disruption, but not in cells with intact *MAP3K7*, largely through downregulation of homologous recombination factors. Overall, the data demonstrate proof of concept for the use of computational approaches to identify druggable targets in cancers driven by loss of tumor suppressors, and nominate a new approach to treating prostate cancers with *MAP3K7* loss.

Abemaciclib Is Potent in PDAC and Synergizes with HuRi/YAP1i

Dhir *et al.* Page 2029

Pancreatic ductal adenocarcinomas (PDAC) are highly proliferative, aggressive tumors, and standard chemotherapeutic interventions have limited efficacy for most patients. Here, Dhir and colleagues demonstrate PDAC cell vulnerability to the CDK4/6 inhibitor abemaciclib, which was associated with reduced cell proliferation and the induction of senescence both *in vitro* and *in vivo*. Additionally, co-targeting of CDK4/6 and related cell cycle pathways via genetic ablation or pharmacological inhibition of HuR and YAP1 produced synergistic effects. Moreover, abemaciclib-resistant cell lines were shown to be cross-resistant to genotoxic chemotherapeutics but not to HuR or YAP1 inhibitors. Taken together, the data nominate new druggable targets for development in PDAC, and form the basis for clinical trials of cell cycle inhibitors both alone and in combination.

Pol β Variant D160G Is Sensitive to Cisplatin

Wang *et al.* Page 2077

Cisplatin therapy is commonly used in the clinical management of cancer, but many tumors exhibit *de novo* or acquired resistance to platinum-based therapeutics via enhanced DNA damage repair (DDR) pathway activity. Here, Wang and colleagues demonstrate that the D160G mutation in DNA polymerase β (pol β), a key mediator of the base excision repair pathway, functions to enhance cisplatin efficacy by impeding the recruitment of other DDR regulators to sites of DNA cross-linkage. Molecular architecture modeling indicated that the D160G mutation increased the DNA binding affinity of pol β, thereby preventing the nucleotide excision repair mediator XPA from binding to sites of DNA damage. Therefore, the authors suggest that activation of pol β D160G may represent a novel neoadjuvant approach to enhancing the efficacy of cisplatin treatment.

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