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Germline Mutations in the CDKN2B Tumor Suppressor Gene Predispose to Renal Cell Carcinoma ......................723


Précis: Germline inactivating mutations in CDKN2B were identified in patients with inherited renal cell carcinoma and predicted to impair its tumor suppressive activity.

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Shen and colleagues identified ARID1A, a subunit of SWI/SNF chromatin remodeling complexes, as a binding partner of ATR, a key regulator of the DNA damage response. ARID1A is recruited to DNA double-strand breaks (DSB) in an ATR-dependent manner and promotes efficient DSB end resection, which is necessary for activation of ATR and subsequent initiation and maintenance of the G2/M checkpoint. ARID1A loss impaired homologous recombination and single-strand annealing DSB repair mechanisms and, similar to loss of BRCA1 or BRCA2, conferred sensitivity to DSB-inducing PARP inhibitors. Given that inactivating mutations in ARID1A are among the most frequent genetic events in human cancers, these findings suggest that PARP inhibitors may be effective in a broader spectrum of cancers than previously appreciated. For details, please see the article by Shen and colleagues on page 752.