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Therapeutic vulnerabilities in ARID1A-deficient cancer

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ARID1A is a component of an evolutionarily conserved chromatin remodeling complex SWI/SNF. Recent genomic data revealed that ARID1A is one of the most frequently mutated genes in a wide spectrum of human cancers. However ARID1A gene itself is not an ideal drug candidate because the majority of ARID1A mutations are inactivating leading to loss of ARID1A expression and ARID1A-SWI/SNF is important for maintaining normal cellular processes. Therefore, a key question is to identify druggable molecular consequences induced by ARID1A deficiency, which can create therapeutic vulnerabilities in ARID1A-mutant tumors. To answer this question, we conducted proteomic analysis of The Cancer Genome Atlas (TCGA) and found that ARID1A deficiency leads to increased expression and activation of DNA damage checkpoint kinase CHK2. Our studies demonstrate a chromatin-independent function of ARID1A in regulating ubiquitination process and indicate that CHK1/2 inhibitors can be an effective therapeutic option specifically targeting ARID1A-deficient human cancers. Most recently, we conducted mutation spectrum analyses of TCGA datasets further revealed enrichment of ARID1A mutations in tumors with a microsatellite instability (MSI) genomic signature and a predominant C>T mutation pattern and significantly increased mutation load in ARID1A-mutant tumors across multiple cancer lineages, supporting ARID1A loss as contributing to defective MMR. Moreover, we found that ARID1A depletion conferred an aggressive tumor phenotype and an increased mutation load. Notably, treatment with anti-PD-L1 antibody reduced tumor burden and prolonged survival of mice bearing ARID1A-deficient but not ARID1A-wild-type tumors.

Biography

Guang Peng is an associate professor in the Department of Clinical Cancer Prevention at The University of Texas MD Anderson Cancer Center. The long-term goal of her research is to characterize and target molecular regulators of the mutational and dysfunctional DNA repair processes driving tumor evolvability and immune responses. One of her major interests is to study the role of ARID1A, one of the most frequenct mutated genes in human cancer, in regulating DNA damage response and DNA repair. Her research has been funded by several agents including National Cancer Institute (NIH), Department of Defense, American Association for Cancer Research, Susan Komen Foundation and Cancer Prevention Research Institute of Texas.

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