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EDITORIAL

Targeting the Metabolic Vulnerability of ARID1A-Deficient Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the major form of primary liver cancer that arises from the transformed hepatocyte. Therapeutic options of advanced HCC are very limited; tyrosine kinase inhibitors and immune-checkpoint inhibitors currently are the mainstay treatments. However, HCC is a heterogeneous disease. The therapeutic outcomes of current HCC therapies remain unsatisfactory. Effective biomarkers to guide therapeutic decisions are urgently needed. Previous studies using whole-genome and -exome sequencing had defined the mutational landscapes of human HCCs. Apart from the frequent mutations on TERT, TP53, and CTNNB1 pathways, ARID1A was identified as a new driver of HCC development.[1] ARID1A is a core subunit of the SWI/SNF complex, which is involved in the chromatin remodeling and epigenetic regulation of gene expression. Somatic mutations of ARID1A have been identified in around 10% of patients with HCC. However, the molecular mechanisms related to ARID1A-associated liver carcinogenesis remain to be further investigated.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Zhang et al[2] studied the functions and therapeutic implications of ARID1A in human HCC. They found that ARID1A is frequently downregulated at the protein level and associated with shorter overall and disease-free survival rates of patients with HCC. Interestingly, the authors found that knockout of ARID1A did not promote the proliferation of HCC cell lines in the normal culture condition but empowered the HCC cells to grow in a glucose-deprived condition. Further investigations revealed that ARID1A interacted with HDAC1 through its C-terminal DUF3518 domain and recruited HDAC1 to the promoter of the USP9X gene. This interaction could be abolished by ARID1A-1989* mutation found in clinical HCC samples. The binding of ARID1A and HDAC1 suppressed the expression of USP9X in HCC. Loss of ARID1A or ARID1A-1989* mutation mitigated the HDAC1-mediated epigenetic silencing and enhanced H3K9 and H3K27 acetylation at the USP9X promoter. USP9X is a deubiquitylating enzyme. Upregulation of USP9X reduces the ubiquitination-associated protein degradation and stabilizes its substrates. AMPKα2, an isoform of the α subunit of AMPK, has been identified as a substrate of USP9X. They found that USP9X mediated deubiquitination of AMPKα2 at the K364 residue. USP9X inhibitor WP1130 and loss-of-function USP9X mutation augmented the ubiquitination of AMPKα2. Consistently, knockdown of USP9X inhibited the expression of AMPKα2 in HCC cells. In human HCC, ARID1A expression was negatively correlated with USP9X and AMPKα2. Moreover, the ARID1A^{low}AMPKα2^{high} group HCC had a shorter overall survival when compared with the ARID1A^{high}AMPKα2^{low} group. AMPK signaling is a key energy sensing pathway. AMPK is activated on glucose starvation, which regulates multiple metabolic pathways, such as glycolysis, lipid metabolism, and antioxidant production, to allow HCC cells to adapt to the glucose-depleted condition. Thus, the identification of the ARID1A/HDAC1/USP9X/AMPK axis explained why the loss of ARID1A provided a growth advantage to HCC cells under the glucose-deprived condition. Importantly, Zhang et al[2] demonstrated a synthetic lethality between ARID1A deficiency and AMPK inactivation in HCC. Treatment of AMPK inhibitor, Compound C, suppressed HCC growth in orthotopic implantation model in nude mice. Interestingly, ARID1A knockout cells were more sensitive to Compound C treatment and exhibited a prolonged survival of tumor-bearing mice. Thus, Zhang et al[2] delineated a novel ARID1A/HDAC1/USP9X/AMPK axis that might be important for HCC development and progression. They also demonstrated a possibility of targeting the metabolic vulnerability of ARID1A-deficient HCC cells by AMPK inhibitor. The findings of Zhang et al[2] linked the epigenetic regulatory function of ARID1A to cancer metabolism, which significantly enhances the understanding of the molecular mechanisms of ARID1A-related HCC. The findings also highlighted that ARID1A deficiency might be a potential biomarker for precision HCC treatment.

Nevertheless, several outstanding questions remain to be further clarified by future studies. First, in contrast to the frequent downregulation of ARID1A protein, ARID1A mRNA is significantly upregulated in human HCC tumors when compared with the nontumorous liver samples as revealed by the RNA-seq data of TCGA HCC cohort. This observation implies that ARID1A expression is tightly regulated at the posttranscriptional or posttranslational levels. Future studies should investigate the mechanisms related to ARID1A protein translation and turnover. Deregulation of these regulatory mechanisms may contribute to ARID1A-related liver carcinogenesis. Second, ARID1A-deficient cells might reprogram their metabolic pathways and use other energy source to generate ATP, antioxidant, and metabolite intermediates under glucose-deprived conditions. Further research should delineate the metabolic profiles of ARID1A-wild-type and -deficient HCCs to better understand the metabolic vulnerabilities of ARID1A-deficient HCC. Finally, AMPK has been reported to be inactivated in human HCC. AMPK activator metformin also exhibits anticancer effects on different cancers, including HCC.[3] These notions contradict the findings of Zhang et al.[2] The heterogeneous context of HCC may be a possible explanation to this paradox. AMPK

might serve as an oncogene in glucose-deprived HCC but acts as a tumor suppressor in other HCC subtypes. Future studies should reconcile these inconsistent findings and clarify the roles of AMPK signaling in HCC.

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Conflicts of interest
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