mTOR-Dependent ARID1A Degradation: A New Twist in the Genetic–Epigenetic Interplay Driving Hepatocellular Carcinoma

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The importance of the cross-talk between the genetic and epigenetic alterations promoting cancer development is well understood; however, the molecular details underlying the mechanism of how oncogenic signaling remodels the epigenome to generate a procancer transcriptome require further elucidation. The study by Zhang and colleagues in this issue of *Cancer Research* reveals a novel role for oncogenic mTOR signaling leading to the degradation of a prominent chromatin remodeler, ARID1a, establishing an altered, protumor chromatin landscape in hepatocellular carcinoma (HCC) controlling tumor development and treatment resistance. These findings highlight oncogenic effects on chromatin remodelers as an important factor in both HCC pathobiology and therapeutic response. As strategies for cancer therapy begin to move in an increasingly individualized direction, increased knowledge into the impact of restoring the function of chromatin remodelers on response to therapy is warranted.

See related article by Zhang et al., p. 5652

The initiation and development of cancers including hepatocellular carcinoma (HCC) requires multiple somatic mutations that convey prosurvival, proliferative, and invasive properties to the transformed cell. Commonly mutated pathways involve activating mutations in mitogenic signaling cascades and inactivating mutations of tumor suppressors regulating genome stability and cell growth programs (1). Hand-in-hand with these mutations, epigenetic modifications that lead to an aberrant transcriptome that aids the transformation process are essential for the development of cancers (2–4). Beyond the regulation of gene expression, histone modifications and chromatin remodeling are integral to DNA damage repair (5, 6). Mutations in epigenetic effectors result in the breakdown of DNA repair, which in turn drives the accumulation of mutations and a cycle of genomic instability, a hallmark of cancer (7, 8). Although the genetic–epigenetic interplay is well-studied, there remain important gaps in knowledge pertaining to the mechanistic interaction between these genetic events and their regulation of the epigenome. In this issue, Zhang and colleagues demonstrate experimentally that hyperactive signaling from oncogenic mTOR pathway initiates the degradation of ARID1a, a key chromatin remodeling complex protein (9). This loss of ARID1a permits genomic access to the transcriptional regulator, YAP, eliciting a YAP-dependent transcriptome that allows for expanded cell growth and tumor development (**Fig. 1**). Furthermore, the authors establish that mTORC1-mediated ARID1a degradation conveys resistance to rapamycin, an insight with consequences for individualized cancer therapies beyond HCC.

The authors analyzed genomic and proteomic datasets from The Cancer Genome Atlas and the NCI, respectively, and showed mTOR signaling pathway and SWI/SNF chromatin remodeling complex mutations were mutually exclusive in HCC, suggesting a functional interplay between the two. Focusing on ARID1a, which is often mutated in HCC and is an integral member of the SWI/SNF chromatin remodeling complex, the authors discovered an inverse relation between ARID1a protein expression and expression of markers of mTOR signaling pathway activity, p-AKT and p-S6K, in a human HCC proteomics dataset, suggesting an antagonistic relationship between mTOR signaling and ARID1a protein expression. Biochemical analysis in HCC cells confirmed this relationship and established that mTORC1 signaling triggered ARID1a proteasomal degradation via SCF-mediated K48 polyubiquitination *in vitro*. Seeking to determine the biological significance of ARID1a depletion on HCC *in vivo*, the authors developed a mouse model of HCC through hydrodynamic transfection, which resulted in stable expression of NRAS/AKT and either ARID1a overexpression or ARID1a knockdown. Depletion of ARID1a *in vivo* resulted in accelerated tumor growth and decreased survival, while ARID1a overexpression had the opposite effect, increasing survival and slowing tumor growth. Through this series of experiments, the authors establish not only that oncogenic mTOR signaling leads directly to the modulation of chromatin remodeling by inducing degradation of ARID1a, but also that this modulation is a key event that allows for tumor development and progression.

Understanding that mTORC1-dependent degradation of ARID1a likely had effects on both chromatin accessibility and transcriptional programs, the authors integrated assay for transposase-accessible chromatin using sequencing and RNA sequencing from rapamycin-treated and nontreated HCC cells. The Hippo–YAP signaling pathway was identified as the predominant beneficiary of mTORC1-mediated ARID1a degradation. Furthermore, YAP occupancy at transcriptional start sites of canonical YAP-regulated genes, *CTGF* and *CYR61*, was lost by rapamycin treatment and knockdown of ARID1a reversed this effect, demonstrating that ARID1a depletion facilitates YAP binding. Seeking to determine how chromatin remodeling complex mutational status affects HCC response to therapeutics targeting mTOR signaling, the authors mined the Cancer Cell Line Encyclopedia and the Genomics of Drug Sensitivity in Cancer datasets for cell lines with chromatin

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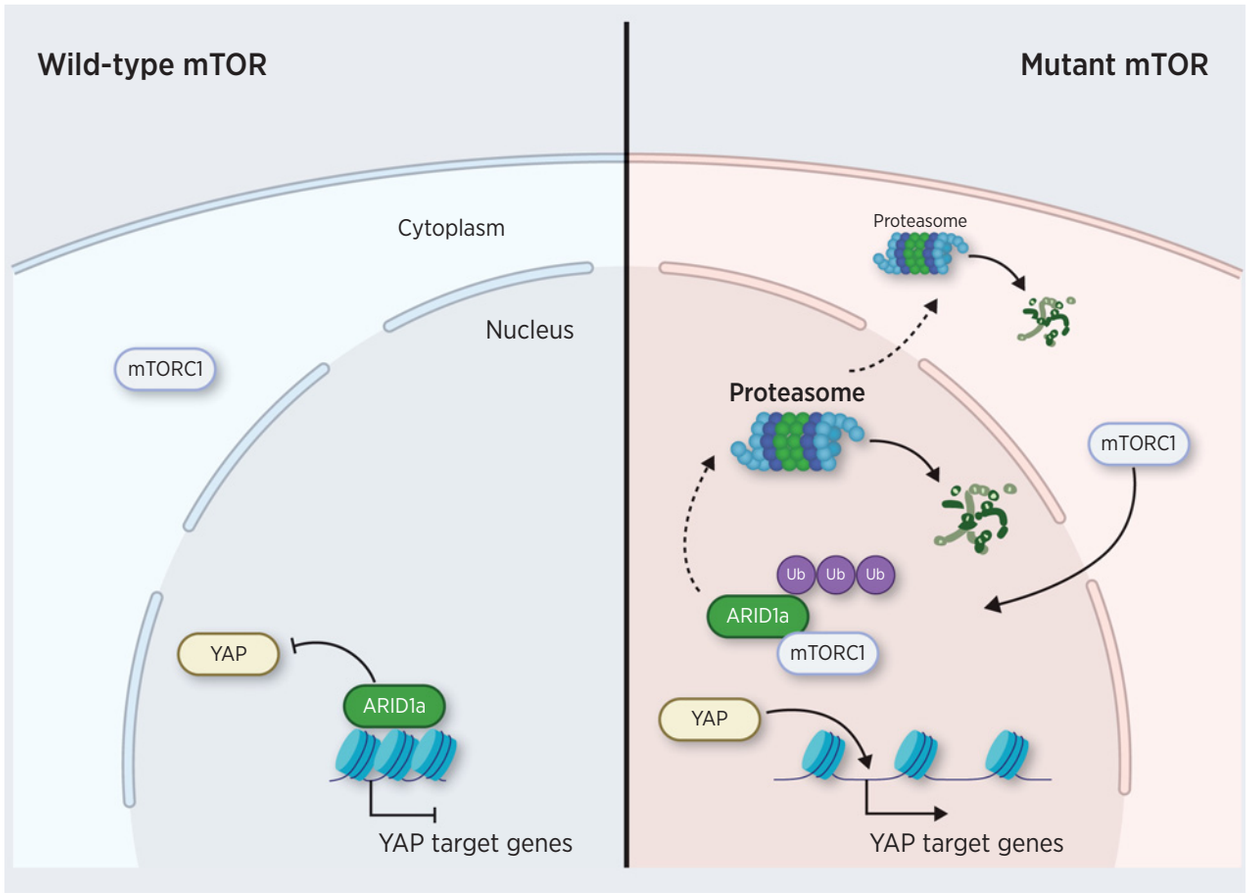

Figure 1.
mTORC1-mediated proteasomal degradation of ARID1a leads to YAP-dependent transcription. In HCC cells carrying wild-type mTOR, ARID1a inhibits YAP binding by regulating chromatin conformation. The constitutively active mutant mTOR (mTORC1) enters the nucleus and promotes the polyubiquitination and proteasomal degradation of ARID1a. Loss of ARID1a leaves chromatin permissive to YAP binding, leading to transcription of YAP-dependent genes.

remodeling complex mutations and their corresponding sensitivity to temsirolimus, a rapalog. This analysis, further substantiated with *in vitro* proliferation assays in rapamycin-treated ARID1a-mutant and wild-type HCC cells, showed that chromatin remodeling complex mutations have the propensity to confer resistance to mTOR signaling inhibitors in culture models of HCC. Integration of these genetic and epigenetic data establishes that the loss of tumor suppressing chromatin remodeling factors either by direct inactivating mutation, or more interestingly via effects of oncogenic signaling, both engenders an epigenome permissive to a procancer transcriptome and grants resistance to HCC-targeted therapies.

In all, this study provides much needed insight into the mechanism by which oncogenic signaling leads to epigenomic rewiring observed during transformation. mTORC1-mediated degradation of ARID1a highlights the complex and dynamic epigenetic regulation of transcription during transformation. This study is the first to attribute directed degradation of a chromatin remodeler to oncogenic mTOR and, as activating PI3K–AKT–mTOR signaling axis mutations occur in nearly all solid tumors, has broad implications outside of HCC (10). It also opens the door for investigation of similar mechanisms induced by other commonly mutated mitogenic signaling pathways, such as oncogenic RAS. A key insight, outside of the mTORC1-ARID1a mechanism itself, is the observation and experimental corroboration that a change in chromatin remodeling function leads to resistance to rapamycin and rapalogs. Zhang and colleagues' discovery that resistance to HCC therapeutics can be driven by the functional status of chromatin remodeling proteins highlights the benefits of broadening the scope of information utilized for individualized selection of therapies.

Authors' Disclosures

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