# Loss of ARID1A protein drives onset and progress of colon cancer

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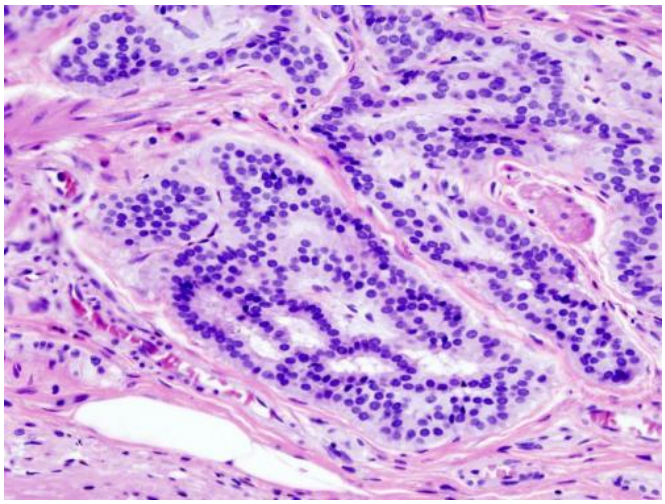

Cancer — Histopathologic image of colonic carcinoid.
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A team of scientists has developed a model system in mice that allows them to look closely at how a protein often mutated in human cancer exerts its tumor-silencing effects. Not all cancers are caused by direct changes in the genetic code. Cancers also arise from epigenetic events that influence gene expression in other ways. The new findings, reported online in *Nature Genetics*, shed light on how epigenetic processes contribute to gene regulation and the onset of colon cancer.

"ARID1A mutations occur in a broad range of human cancers, and it is important to have experimental systems where we can look at how mutation of this gene contributes to disease," said Charles W. M. Roberts, M.D., Ph.D., corresponding author of the study and executive vice president and director of the Comprehensive Cancer Center at St. Jude Children's Research Hospital. "Our results represent an advance in modeling colon cancer and implicate enhancer-mediated gene regulation as a principal tumor suppressor function of ARID1A."

ARID1A is a component of the SWI/SNF chromatin remodeling complex. Chromatin remodeling, which controls how much "read access" the cellular transcription machinery has to DNA sequences, can have profound consequences on gene expression. Genes encoding chromatin remodeling proteins are some of the most frequently mutated genes in human cancer.

The researchers showed that ARID1A functions as a tumor suppressor in the colon of mice but not in the small intestine. They discovered that enhancers, short regions of DNA that specify which genes are turned on in each cell type, were an important part of the interaction of ARID1A with the SWI/SNF chromatin remodeling complex.

Peter J. Park of Harvard Medical School and one of the authors of the study remarked: "Our work showed that when ARID1A is absent, the SWI/SNF chromatin remodeling complex is lost from thousands of enhancers, resulting in reduced expression of nearby genes."

The scientists revealed a broad role for ARID1A in regulating active enhancers whereby loss of ARID1A impairs control of cell identity in the colon and promotes cancer formation.

The new system will be useful in future work. "The system we have developed will be extremely useful to understand why chromatin remodelers are so frequently mutated in cancer, to reveal mechanisms that cause colon cancer growth, and to study potential therapeutic interventions," said Roberts.

**More information:** ARID1A loss impairs enhancer-mediated gene regulation and drives colon cancer in mice, *Nature Genetics*, nature.com/articles/doi:10.1038/ng.3744

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