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Study links BAP1 protein to tumor suppression in kidney, eye, bile duct and mesothelioma cancers

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Researchers at The University of Texas MD Anderson Cancer Center have shown how BRCA-associated protein 1 (BAP1) serves as a tumor suppressor gene in kidney, eye, bile duct, mesothelioma and other cancers by regulating a form of cell death called ferroptosis, opening up a potential new area of therapy research. Findings from the study, led by Boyi Gan, Ph.D., associate professor, Department of Experimental Radiation Oncology, were published in the Sept. 10 online issue of *Nature Cell Biology*.

"Although BAP1 is frequently mutated or deleted in a variety of cancers, the process by which it suppresses tumors remains unclear," said Gan. "Our study achieved a comprehensive identification of BAP1-regulated target genes and relevant biological processes in cancer cells, and identified a BAP1-mediated epigenetic mechanism linking ferroptosis to tumor suppression."

Ferroptosis is a recently identified form of regulated cell death caused by depletion of cystine, an amino acid vital to cancer cell growth and survival, and by overproduction of molecular carriers of oxygen known as reactive oxygen species (ROS) on lipids, which have been linked to cancer and are targets of some therapies.

"Ferroptosis is structurally, genetically and biochemically distinct from other forms of regulated cell death such as apopotosis," said Gan. "It is

well established that cell death, most notably apoptosis, plays important roles in tumor suppression. The roles of and regulatory mechanisms of ferroptosis in tumor biology, however, still remain largely unexplored."

Gan's team described how BAP1 encodes a key enzyme which interacts with other enzymes and cellular components to regulate genes, resulting in tumor suppression via ferroptosis. The researchers found that treatment with a ROS inducer resulted in substantially more ferropotosis-related cell death in BAP1 cancer cells than in other similar cancer cells which do not express BAP1. They also discovered that BAP1 promotes ferroptosis by mediating repression of a cystine 'transporter' called SLC7A11.

"We showed that BAP1 inhibits tumor development partly through SLC7A11 and ferroptosis and that cancer-associated BAP1 mutants lose their abilities to repress SLC7A11 and to promote ferroptosis," said Gan. "Together, our results uncover a previously unappreciated mechanism coupling ferroptosis to tumor suppression."

More information: BAP1 links metabolic regulation of ferroptosis to tumour suppression, *Nature Cell Biology* (2018). DOI: 10.1038/s41556-018-0178-0 , www.nature.com/articles/s41556-018-0178-0

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