Molecular relative of p53 tumor suppressor protein also helps cancer cells thrive

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TAp73, a structural homologue of the tumor suppressor p53, supports tumor cell proliferation by promoting biosynthesis and antioxidant defense. Shown are TAp73-wild-type and TAp73-deficient cells grown on plates under different conditions and stained with crystal violet for their viability. Credit: Art work by Lili Guo, Perelman School of Medicine, University of Pennsylvania

They say you can pick your friends, but not your family. The same may hold true for related proteins. The protein TAp73 is a relative of the well-known, tumor-suppressor protein p53. It shares extensive common gene sequences with p53 and, as suggested by some previous studies, it may function similar to p53 to prevent tumor formation. However, unlike p53, which is the most commonly mutated gene in human tumors, TAp73 is rarely mutated, and instead is frequently overexpressed in a wide range of human tumors, including breast, colon, lung, stomach, ovarian, bladder, liver, neuroblastoma, glioma, and leukemias. In other words, cancer cells may have too many copies of the TAp73 gene.

Researchers still do not know whether TAp73 enhances tumor cell growth and, if so, exactly how it may give an advantage to tumor cells. But, in a new study that appears in *Nature Cell Biology*, Xiaolu Yang, PhD, professor of Cancer Biology at the Perelman School of Medicine, University of Pennsylvania, and the Abramson Family Cancer Research Institute, and colleagues found that TAp73 supports the proliferation of human and mouse tumor cells. They also identify an important mechanism by which TAp73 gives tumor cells a growth advantage: it activates the expression of an enzyme called glucose-6-phosphate dehydrogenase (G6PD), the rate-limiting molecule of the pentose phosphate pathway (PPP).

To fuel the proliferation of tumor cells, their metabolic pathways are fundamentally reprogrammed. This reprogramming allows for rapid generation of macromolecules such as nucleic acids, lipids, and proteins. It also enables tumor cells to reduce the oxidative stresses they experience. The PPP is important for both biosynthesis and anti-oxidant defense, and tumor cells need this pathway for their high rate of replication.

The study was led by Peng Jiang, PhD, and Wenjing Du, PhD, two postdoctoral fellows in the Yang lab. They and the rest of the team found that by stimulating G6PD, TAp73 increases PPP activity and directs the sugar glucose to pathways for synthesizing macromolecules for replication and detoxifying reactive types of oxygen molecules to protect cells from harm.

The team also found that the decrease in

replication in cells without TAp73 can be rescued by either enforced expression of G6PD, or adding basic molecules called nucleosides (the precursor for nucleic acids) and a reactive oxygen species scavenger to mop up these deleterious molecules, two outcomes of the PPP. These data provide the evidence that stimulating the PPP is a main proliferative effect of TAp73.

This is the first evidence that TAp73 is needed for tumor growth, as seen in the mouse and human colon, lung and other cancers studied.

Previous work by Yang's lab, also led by Jiang and Du, found that p53 has the exact opposite effect on the PPP. They found that p53 physically binds to and inhibits G6PD. Through this inhibition, p53 normally dampens synthesis of molecules and cell reproduction by forcing the cell to take up less glucose. If p53 can't do its intended job, cells grow out of control. In tumors, more than half of which carry mutations in the p53 gene, this routing function is abolished, enabling cells to build biomass and divide with abandon. The opposing effect of two members of the p53 family on the G6PD underlines this importance of this enzymes and the pathway it controls, the PPP, in tumor cells.

"These findings establish a critical role for TAp73 in regulating metabolism and connect TAp73 and the PPP to cancerous cell growth," says Yang.

The prevalence of p53 inactivation and TAp73 up-regulation indicate that modulating the pathways that these two proteins control could bring substantial benefit to tumor therapy. However, targeting these pathways has proven to be difficult as most proteins in the p53 and TAp73 pathway operate via protein-protein interactions, which are generally poor drug targets.

In contrast, metabolic enzymes are among the best drug targets. The identification of G6PD as an enzyme that becomes hyper-activate in tumors with p53 inactivation and/or TAp73 over-expression, two of the most common genetic alterations in cancer cells, suggests inhibition of this enzyme, or its related enzyme in the PPP pathway, may be highly beneficial for the therapy of a wide range of tumors. The Yang lab has previously identified another set of enzymes that are both regulators and responders of p53. They hope that their work will give a strong impetus for developing high specific compounds for p53 and TAp73-regulated enzymes and testing them for cancer therapy, says Yang

More information:
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