MedicalXpress

Cancer suppressor gene links metabolism with cellular aging

January 13 2013

The tumor suppressor protein p53 is an attractive target for drug developers. But this path has so far proven difficult, as most p53 regulatory proteins operate via protein-protein interactions, which make for poor drug targets, as opposed to ones based on enzymes. Now, researchers have identified a class of p53 target genes and regulatory molecules that represent more promising therapeutic candidates.

It is perhaps impossible to overstate the importance of the tumor suppressor gene p53. It is the single most frequently mutated gene in human tumors. p53 keeps pre-cancerous cells in check by causing cells, among other things, to become senescent – aging at the cellular level. Loss of p53 causes cells to ignore the cellular signals that would normally make mutant or damaged cells die or stop growing.

In short, the p53 pathway is an obvious and attractive target for drug developers. But that strategy has so far proven difficult, as most p53 regulatory proteins operate via protein-protein interactions, which make for poor drug targets, as opposed to ones based on enzymes.

Now, a team of researchers from the Perelman School of Medicine, University of Pennsylvania, has identified a class of p53 target genes and regulatory molecules that represent more promising therapeutic candidates.

As Xiaolu Yang, PhD, professor of Cancer Biology and investigator in Penn's Abramson Family Cancer Research Institute, and his team

describe in an advance online *Nature* publication, p53 participates in a molecular feedback circuit with malic enzymes, thereby showing that p53 activity is also involved in regulating metabolism.(The Yang lab identified p53's role in glucose metabolism in the past.)

The new findings, Yang says, suggest that p53 acts as a molecular sensor of metabolic stress and explains how metabolic stress can lead to senescence in cells.

"We uncovered an important regulatory mechanism for p53 as well as an effector mechanism for p53," Yang says.

Significantly, the findings also identify malic enzymes as novel and potentially useful pharmaceutical targets for anticancer therapy, as well as possible mediators of the normal aging process – though neither possibility was actually addressed in the current study.

As cells become damaged and precancerous, the p53 protein prevents those cells from continuing towards becoming tumors by causing the cells to senesce. Metabolic cues also regulate senescence, but the molecular relays coupling those two processes—senescence and metabolism—remained unknown.

Yang and his team decided to test if a pair of enzymes, malic enzyme 1 and malic enzyme 2 (ME1 and ME2), could be involved. Malic enzymes recycle malate – an intermediate molecule – back into an end-product of glycolysis – pyruvate – storing energy in the process. Malic enzymes are important for adjusting metabolic flux to suit proliferating cells' demands for energy and biosynthesis. Thus, these two enzymes are attuned to the energy and proliferative state of the cell.

Yang's team found that p53 inhibits malic enzyme expression, such that loss of p53 causes malic enzyme abundance to increase. Conversely,

malic enzymes keep p53 in check; loss of malic enzymes ramps up p53 activation and induces senescence via either downregulation of a p53 inhibitor (Mdm2) or production of oxygen radicals. Overexpression of malic enzymes inhibits senescence.

The result, Yang explains, is a "feed-forward loop" in which activation of p53 suppresses malic enzyme expression, reducing malic enzyme levels and further upregulating p53, leading to senescence. On the other hand, upregulation of malic enzymes inhibits p53. p53 inhibition loosens the protein's grip on malic enzyme expression, allowing malic enzyme levels to rise.

"This is a circuit," he says. "Going around this loop, you get pretty robust activation."

These same results played out in animal models described in the *Nature* study. Loss of either ME1 or ME2 reduced tumor weight, even with p53-null tumor cells, which suggests an additional, p53-independent function of malic enzymes.And, overexpression of malic enzymes led to more substantial tumors.

According to Yang, the study pegs malic enzymes as molecular players linking senescence and metabolic state. Those enzymes could potentially serve as anticancer drug targets, he says. But equally important, they may also play a role in the normal process of cellular aging.

"Senescence is aging at the cellular level," says Yang, who notes that considerable research has demonstrated a correlation between caloric restriction and lifespan. "We may have identified a good starting point to understand how aging works."

Provided by University of Pennsylvania School of Medicine

Citation: Cancer suppressor gene links metabolism with cellular aging (2013, January 13) retrieved 5 May 2024 from https://medicalxpress.com/news/2013-01-cancer-suppressor-gene-links-metabolism.html

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