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Cell energy sensor mechanism discovered: Studies linked to better understanding of cancer drugs

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Johns Hopkins and National Taiwan University researchers have discovered more details about how an energy sensing "thermostat" protein determines whether cells will store or use their energy reserves.

In a report in the Feb. 9 edition of *Nature*, the researchers showed that a chemical modification on the thermostat protein changes how it's controlled. Without the modification, cells use stored energy, and with it, they default to stockpiling resources. When cells don't properly allocate their energy supply, they can die off or become cancerous. The Johns Hopkins team focused especially on enzymes that add or remove so-called acetyl groups from protein molecules.

"Understanding how cells are affected by adding acetyl groups to proteins, particularly those involved in energy use, is important because there is increasing use of drugs that block acetyl-removing enzymes for treatment of cancer and neurodegenerative diseases," says Jef Boeke, Ph.D., professor of molecular biology, genetics and oncology, and director of the High Throughput Biology Center at the Johns Hopkins University School of Medicine. "Blocking acetyl-removing enzymes turns on anticancer genes that help fight cancer; however, it is not known what other genes and cellular processes may also be affected by these treatments."

To determine which enzymes remove acetyl chemical groups from

which proteins, the researchers engineered human cells with reduced levels of each of 12 enzymes known to remove acetyl chemical groups. In each of these cell lines, they then turned down each of about 20,000 genes and used a DNA "chip" to identify which genes were affected by reduced levels of the acetyl-removing enzymes. The DNA chip highlighted a specific interaction between the thermostat protein, AMP-activated protein kinase (AMPK), and one of the acetyl-removing enzymes, HDAC1.

With less HDAC, AMPK was turned "off," presumably because it retains its acetyl group, the researchers concluded. AMPK acts like an energy thermostat because when energy levels are low in the cell, AMPK kick-starts processes that use the cell's energy reserves and cuts off reactions that store energy. On the other hand, when the cell has plenty of energy, AMPK turns off, causing energy in the form of sugar and fats being stored for later use.

Because the HDAC1 protein turned on AMPK, the researchers presumed there would be a corresponding acetyl-adding enzyme to specifically turn off AMPK. To find this enzyme, they extracted AMPK protein from eight different cell lines, each with reduced levels of a type of acetyl-adding enzyme. They found that AMPK in cells with reduced levels of this acetyl-adding enzyme, called p300, was less acetylated than in cells containing normal amounts of p300.

To confirm the idea that adding or removing acetyl groups directly affects how AMPK controls the way the cell uses energy, they measured the cell's energy stores with the help of a dye that accumulates in the fat globules of a cell. The dye let them estimate the size of fat globules that store energy. The cells unable to add acetyl to AMPK contained less of the dye and therefore smaller fat globules compared to normal human cells. Conversely, the cells unable to remove acetyl groups from AMPK contained more of the dye, indicating bigger fat globules. The research

team concluded that when AMPK contains acetyl groups the cell uses less of its energy reserves than when AMPK does not contain acetyl groups.

Boeke says the work on human cells followed similar studies on yeast energy proteins done earlier in his laboratory.

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