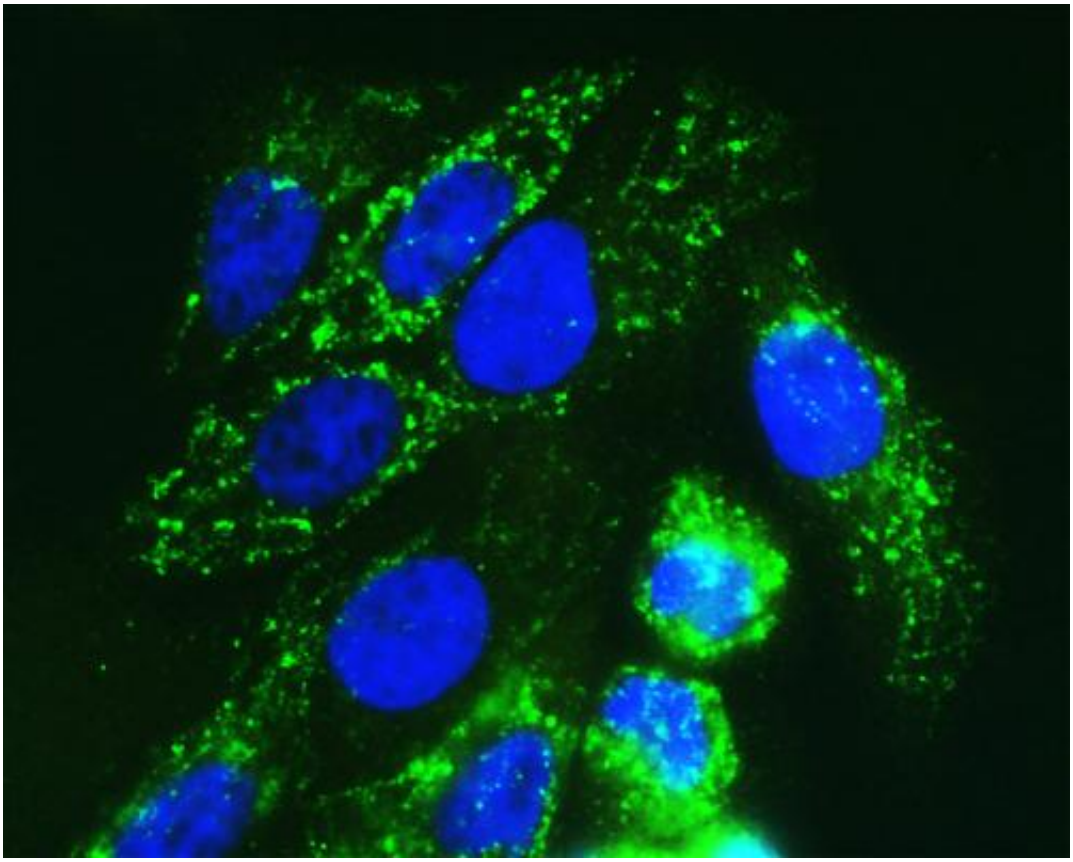
Cancer cell metabolism kills

April 15 2013



Scientists have discovered that low levels of ATP make cancer gene expressing cells suicidal. Declining ATP levels activate a cellular energy sensor AMPK, which adds a phosphate group to tumor suppressor protein p53, extending the protein's lifetime. This form of p53 moves to mitochondria to activate a cell death protein Bak, which renders cells sensitive to apoptosis. In this immunofluorescence microscope image of cancer gene Myc expressing cells, active death protein Bak appears as green spots localizing on the surface of the mitochondria. The blue staining marks the cell nuclei. Credit: University of Helsinki

Adenosine-5'-triphosphate (ATP) is the main energy source for all forms of work inside our cells. Scientists from the University of Helsinki, Finland, have found that even a short-term shortage of ATP supply can be fatal for cancer cells because activation of a mitochondria-addressed cell death pathway.

ATP is the main energy currency of cells and one might expect that not only contracting muscle, but also uncontrollably dividing cancer cells would have a high demand for ATP. However, for some reason cancer cells have re-programmed their metabolic engines to produce less ATP. The phenomenon, known as Warburg effect, is typical for cancer cells and the mechanism behind is believed to benefit cancer cells by switching biochemical engines from energy manufacturing reactions to anabolic reactions, which primarily support growth of the cell size and proliferation.

The triggers for "non-stop" proliferation programs in cancer cells are the tumor-promoting oncoproteins, like protein called Myc. Luckily, it seems that oncoproteins are not perfect programmers.

Finnish scientists from the University of Helsinki, investigating how Myc re-engineers metabolic pathways in cells, have identified an unexpected branch in the pathway - a branch that ends to cell death (apoptosis).

The researchers found that Myc activates cancer-like changes in cell metabolism, causing a sudden fall in ATP concentration inside the cells. Declining ATP levels awake a bioenergy sensor protein known as AMP kinase (AMPK), which starts a biochemical chain of events moving a tumor suppressor protein p53 to the surface of the mitochondria. At mitochondria, p53 activates apoptosis-promoting proteins, the investigation suggests.

According to University of Helsinki scientist and Finnish Academy Research Fellow Juha Klefström, PhD, who led the study, "Myc oncoprotein not only boosts tumor cell proliferation but it also makes the cells vulnerable to cell suicide program, apoptosis. The cancer gene dependent vulnerability to apoptosis has promise to be the prime target for future targeted cancer therapies but first, we need to understand the cell pathways that are causing this vulnerability. The investigated connections between Myc, energy metabolism and apoptosis will help us to understand the biochemistry of cancer cell apoptosis. However, the finding is also interesting from a therapeutic standpoint since there are many drug-like molecules that can be used to turn on and off the AMPK controlled pathways in cancer cells."

Healthy cells may encounter ATP and energy shortage for example, during strenuous exercise, so that alone is not sufficient to kill the cells. Why then Myc oncoprotein transformed cells succumb to ATP deprivation?

A graduate student Anni Nieminen, the first author in the study explains, "In healthy cells dwindling ATP levels signals activation of AMPK, which tells the cells to save energy, for example, by stopping the cell proliferation. The resting cells can then restock ATP supplies before entering the energy consuming proliferation again. However, cells with active Myc cannot stop the cell cycle engine and we think that the non-stop proliferation of the cells with low ATP content leads to prolonged activation of AMPK and p53. Gradual increase of p53 levels activates apoptosis promoting protein Bak on the surface of the mitochondria making these cells vulnerable to death. The inability of Myc transformed cells to rest and recover could explain why Myc makes cells so vulnerable to apoptosis."

How can these cancer cell specific metabolic pathways and reactions be targeted with drugs?

According to Juha Klefström, "For example, recent epidemiological studies have shown that a diabetes drug metformin, which acts as an AMPK activator, may reduce the risk of cancer. It is often claimed that a drug-induced AMPK activation starves cancer cells to death. Our study suggests that AMPK can speak directly to the cells' death machinery, which opens new possibilities to exploit the AMPK pathway for cancer therapy."

The study will be published in the *Proceedings of the National Academy of Sciences* (*PNAS*) Online Early Edition on the 15th April, 2013.

More information: Myc-induced AMPK-phospho p53 pathway activates Bak to sensitize mitochondrial apoptosis , www.pnas.org/cgi/doi/10.1073/pnas.1208530110

Provided by University of Helsinki