MicroRNA drives cells' adaptation to low-oxygen living

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Researchers have fresh insight into an evolutionarily ancient way that cells cope when oxygen levels decline, according to a new study in the October 7th issue of *Cell Metabolism*. In studies of cells taken from the lining of human pulmonary arteries, they show that a microRNA - a tiny bit of RNA that regulates the activity of particular genes and thus the availability of certain proteins - allows cells to shift their metabolic gears, in a process known as the Pasteur effect.

While the discovery is a fundamental one, the researchers say it could point to new ways to tackle diseases, including cancer and cardiovascular disease.

"The Pasteur effect is really best defined as the way by which cells adapt to low oxygen concentrations," said Joseph Loscalzo of Brigham and Women's Hospital and Harvard Medical School. Cells do that by switching from mitochondrial metabolism to glycolysis.

Normally, cells produce high-energy molecules such as ATP through components known as mitochondria, he explained. Loscalzo likens mitochondria to little factories that churn out ATP under normal oxygen conditions. If mitochondria continue to operate when oxygen becomes limited, they do so inefficiently, he said, spewing out toxic derivatives of oxygen (including superoxide and hydrogen peroxide) in the process.

"When cells encounter that situation, they need to direct their energy program from one with mitochondria to one that uses less oxygen,"

Loscalzo continued. That secondary program, called glycolysis, doesn't produce as much cellular fuel, but it does so without toxic byproducts.

In the new study, the researchers first went in search of microRNA that rise when cells become hypoxic, meaning that they are deprived of sufficient oxygen. That screen done in many types of cells landed them miR-210 as a key player. Using several methods, they were able to predict that miR-210 would influence activity of iron-sulfur cluster assembly proteins (ISCU1/2). Those proteins act as scaffolds that assist in the assembly of iron-sulfur clusters, important ingredients for mitochondria to function.

The team shows that miR-210 does in fact directly target ISCU1/2, which disrupts the integrity of iron-sulfur clusters. As a result, mitochondrial respiration and associated functions get shut down.

The basic findings may have clinical implications, Loscalzo said, noting that scientists have devised increasingly interesting ways to selectively inhibit microRNAs. For instance, cancer cells typically operate under Pasteur effect conditions (a phenomenon known as the Warburg effect.) The ability allows tumors to grow even when they outstrip their blood supplies and prevents the generation of toxic oxygen derivatives within them.

You could imagine that treatments designed to block miR-210 might hobble tumors by manipulating their usual metabolic profile, Loscalzo said. In other settings, you may want to increase miR-210, he added. Such a therapy may have potential in patients with blocked coronary arteries, for instance.

"The transition of heart muscle to miR-210-dependent glycolysis might be enhanced by administering [the miRNA]," he said. By helping that transition along, physicians might be able to help minimize the

production of toxic byproducts by mitochondria in their patients, and ultimately preserve more heart tissue, Loscalzo adds.

Source: Cell Press (news : web)