



Low-oxygen switch for cells

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Australian researchers have identified a molecular 'switch' that helps our body's cells cope when oxygen levels fall, a finding that could provide the basis for future drugs to help in recovery from stroke and heart attack.

A team from the University of Adelaide's [Molecular Biosciences](#) department and [CSIRO Health Sciences and Nutrition](#) report their findings in this week's issue of *Science*.

"We know all cells in humans need oxygen for reproduction and survival but when oxygen becomes limiting, such as in heart attack, the cells must adapt," said researcher Dr Murray Whitelaw.

"The question has been how do they do it."

It is known that certain genes are activated in low-oxygen conditions. These genes help increase delivery of oxygen by making more red blood cells and blood vessels. They also reduce the body's reliance on oxygen by switching to a form of energy production not dependent on oxygen, called glycolysis (which uses glycogen from the liver).

But how does the body know when to activate these genes?

Previous research has found that a protein known as Hypoxia Inducible Factor (HIF) responds to low oxygen levels and switches on the genes. However, the nuts and bolts of how it does that have to date only been partially understood.

HIF was identified as having two segments (domains) that were involved in the switching process. One segment had been found to be responsible for increasing the amount of HIF in the cell. Under normal circumstances HIF is constantly made and broken down. However researchers have found that under low-oxygen levels, HIF loses a hydroxyl (oxygen and hydrogen) group from a proline amino acid on this domain. This changes the shape of the protein and makes it less likely to be degraded.

The other domain of HIF was known to be responsible for the actual activation of genes that helped cells adapt to low oxygen, however the molecular switch for that has to date been unknown.



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Dr Whitelaw and colleagues found under low-oxygen levels, HIF loses a hydroxyl molecule from an asparagine amino acid on this other domain. This changes the shape of the protein and allows it to activate the genes.

"The finding has implications for treating ischaemic diseases in which tissues are deprived of oxygen because the blood vessels are not functioning correctly," Dr Whitelaw said.

He said his findings could be used to help develop drugs that enhance cells' adaptation to low-oxygen conditions. These drugs would prevent the binding of hydroxyl groups to the HIF protein and in turn boost the amount of the protein around to improve oxygen delivery.

The researchers have patented the asparagine-hydroxyl part of the HIF protein as a possible target for drugs, and will now look for other oxygen-controlled proteins that could be involved in the body's response to low oxygen levels.

Anna Salleh – ABC Science Online

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