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EXPLAINED: HOW DO OXYGEN LEVELS AFFECT CELL METABOLISM?

Relevant for: Science & Technology | Topic: Biotechnology, Genetics & Health related developments

The story so far: This year, the Nobel Prize for Physiology or Medicine was awarded to three scientists, William G. Kaelin Jr. from Howard Hughes Medical Institute, Maryland, U.S., Sir Peter J. Ratcliffe from Francis Crick Institute, London, and Gregg L. Semenza from the Johns Hopkins Institute for Cell Engineering for their discovery of how cells sense and adapt to oxygen availability. The three scientists have uncovered the genetic mechanisms that allow cells to respond to varying levels of oxygen.

Oxygen is used by all cells to convert food to useful energy. While oxygen is essential for the survival of cells, excess or too little oxygen can lead to adverse health consequences.

Oxygen supply temporarily reduces in muscles during intense exercise and under such conditions the cells adapt their metabolism to low oxygen levels. Proper growth of the foetus and placenta depends on the ability of the cells to sense oxygen.

Drugs have already been developed to treat anaemia by making the body produce increased number of red blood cells. Similarly, drugs to increase oxygen availability in people with heart disease and lung cancer are being tested. Many diseases can be treated by increasing the function of a particular pathway of the oxygen-sensing machinery. At the same time, inhibiting or blocking the pathway will have implications in treating cancer, heart attack, stroke and pulmonary hypertension. Cancers are known to hijack the oxygen-regulation machinery to stimulate blood vessel formation and also re-programme the metabolism in order to adapt to low oxygen conditions. The reprogramming of metabolism gives cancer cells the plasticity to shift from a state where they have limited potential to cause cancer to a state when they have greater potential for long-term growth. Efforts are under way to develop drugs that can block the oxygen-sensing machinery of cancer cells to kill them.

The rate at which we respire depends on the amount of oxygen being carried in the blood. Specialised cells present next to large blood vessels in the neck sense the blood oxygen level and alert the brain to increase the rate of respiration when the oxygen level in the blood goes down. This discovery won a Nobel Prize in 1938.

At the beginning of the last century, scientists knew that specialised cells present in the kidneys make and release a hormone called erythropoietin. When oxygen level is low, as in high altitudes, more of this hormone is produced and released, leading to increased production of red blood cells in the bone marrow — helping the body adapt to high altitudes. Besides increasing red blood cells, the body also grows new blood vessels to increase blood supply.

Both Prof. Semenza and Sir Ratcliffe independently studied how the erythropoietin gene is regulated by varying oxygen levels. Both researchers found that the oxygen-sensing mechanism is not restricted to kidneys where the erythropoietin is produced but by diverse cells in tissues other than the kidney. Prof. Semenza identified a pair of genes that express two proteins. When the oxygen level is low, one of the proteins (HIF-1alpha) turns on certain genes, including the erythropoietin gene, to increase the production of erythropoietin. The hormone, in turn, increases the oxygen availability by boosting the production of red blood cells.

Prof. Kaelin Jr., who was studying an inherited syndrome called von Hippel-Lindau’s disease

(VHL disease) found that people had increased risk of cancer when they inherited VHL mutations. He found the VHL gene seemed to be involved in how cells respond to oxygen.

The function of the HIF-1alpha protein, which turns on the genes to produce more erythropoietin, is blocked and is rapidly degraded when the oxygen level is normal but remains intact when oxygen level is low. Sir Ratcliffe found that VHL interacts with the HIF-1alpha protein and degrades it when the oxygen level is normal. This ensures that excess red blood cells are not produced when the oxygen level is normal. In 2001, Prof. Kaelin Jr. and Sir Ratcliffe both elucidated more details on the mechanism of degradation of HIF-1alpha protein by VHL when the oxygen level is normal but not when the oxygen level is low.

Athletes have been found to use erythropoietin, synthetic oxygen carriers and blood transfusions for blood doping. Each of the three substances or methods is banned by the World Anti-Doping Agency (WADA). While the use of erythropoietin in people who are anaemic due to chronic kidney disease helps in increasing the oxygen level in the blood, the use of the hormone by normal, healthy people can lead to serious health risks. In the case of healthy people who have a normal red blood cell count, the use of external erythropoietin is highly likely to make the blood thick (increase viscosity) leading to an increased risk of heart disease, stroke, and cerebral or pulmonary embolism (clot that blocks the flow of blood).

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