DOI: https://doi.org/10.36094/sc.v86.2020.Nobel_Prize_Physiology_or_Medicine.Basu.65

PHYSIOLOGY OR MEDICINE

When we talk of life on Earth, we know how important oxygen is to our survival. Animals and humans need oxygen to convert food into useful energy. The fundamental question of how cells sense oxygen has implications for several biological processes including development of embryo, cancer, stroke, diabetes, and other ischemic diseases. No wonder, this is an important scientific mystery that researchers have been trying to crack for many years. Yet, despite the publication of hundreds of papers on this subject, till recently there was no clear consensus regarding what the cellular oxygen sensor is, or even the number of sensing mechanisms there might be. Now scientists seem to have solved the mystery.

William Kaelin

The Nobel Prize in Physiology or Medicine for 2019 has been awarded to three scientists – cancer researcher William Kaelin of the Dana-Farber Cancer Institute and Harvard Medical School, Boston, Massachusetts, USA; physician-scientist Peter Ratcliffe of the University of Oxford and the Francis Crick Institute, London, England; and geneticist Gregg Semenza of the Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, "for their discoveries of how cells sense and adapt to oxygen availability".

The body's tissues can be deprived of oxygen during exercise or when blood flow is interrupted, such as during a stroke. Cells' ability to sense oxygen is also crucial for the proper growth of a developing foetus and placenta, and also in tumour growth, because the mass of rapidly growing cells can deplete oxygen in the interior of a tumour.

During researches carried out in the 1990s, the three scientists, working independently, revealed the chain of molecular events that allow cells to detect and respond to different levels of oxygen. They had discovered the molecular processes that cells go through to respond to oxygen levels in the body. They found that central to this is a mechanism involving a protein complex called hypoxia-inducible factor (HIF) and a gene called VHL.

The work of the three scientists has helped researchers to understand how the body detects and adapts to low oxygen levels by, for example, making more red blood cells and growing new blood vessels. Their work has established the basis for our understanding of how oxygen levels affect cellular metabolism and physiological function. Their discoveries have also paved the way for promising new strategies to fight anaemia, cancer and many other diseases.

Gregg Semenza

The work of Semenza and Ratcliffe concerned study of the regulation of a hormone called erythropoietin, which is crucial for stimulating the production of red blood cells in response to low levels of oxygen. Semenza and his team identified a pair of genes that encode the two proteins that form HIF and work together to turn on certain genes and boost erythropoietin production when oxygen is low.

Meanwhile, Kaelin's work showed that the VHL gene may also be involved in how cells respond to oxygen, after studying a genetic syndrome called von Hippel-Lindau's disease. This genetic disease leads to dramatically increased risk of certain cancers in families with inherited VHL mutations.

Peter Ratcliffe

Thanks to the ground-breaking work of the three Nobel Laureates, we know much more about how different oxygen levels regulate fundamental physiological processes. Oxygen sensing allows cells to adapt their metabolism to low oxygen levels: for example, in our muscles during intense exercise. Other examples of adaptive processes

controlled by oxygen sensing include the generation of new blood vessels and the production of additional red blood cells. Our immune system and many other physiological functions are also fine-tuned by the oxygen-sensing machinery. Oxygen sensing has also been shown to be essential during foetal development for controlling normal blood vessel formation and placenta development.

The work has led researchers to develop drugs that target oxygen-sensing processes, including drugs for cancer. Drugs that prevent VHL from binding to HIF and causing its degradation are also being investigated as treatments for anaemia and renal failure. Chinese regulators approved the first of these drugs in 2018. ❐

Biman Basu

Dream 2047, November 2019, Vol. 22, No. 2