on this new combination enabled stable charging and discharging, over many cycles for a long period. This invention (1985) led to the construction of a new secondary battery using $LiCoO_2$ as the positive electrode and lithium intercalated carbon as the negative electrode. Yoshino also demonstrated for the first time how to test the safety of the developed batteries. In 2017, Yoshino joined Mejo University as Professor.

Whittingham laid the foundation by systematically developing methods of solid-state electrochemistry to assemble the first prototype rechargeable battery. Goodenough discovered a new compound, lithium cobalt oxide and revolutionized the design of a powerful battery than the early prototype. With Goodenough's cathode as a basis, Yoshino devised the first commercially viable and safe lithium-ion battery by employing petroleum coke, a carbon material that, like the cathode's cobalt oxide, can intercalate lithium ions. It is to be acknowledged here that the three brilliant individuals could not have achieved the success but for the support of the large interdisciplinary team. Goodenough's original lithium cobalt oxide structure is still used in the lithium ion batteries virtually found in every smart phone and tablet around the world. Other variations of the cathode material, lithium manganese oxide designed in his laboratory and refined at Argonne National Laboratory are used in electric cars. His lithium–iron–phosphate cathode is used in many modern power tools.

The Nobel committee, in awarding the prize to 'the trio', called this breakthrough a 'decisive step towards the wireless revolution'.

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# Out of breath: molecular description of cellular responses to hypoxia – 2019 Nobel Prize for Physiology or Medicine

Living organisms need to adapt to changes in the environment in order to ensure their survival. To do this effectively, an essential requirement is the ability to sense changes in environmental conditions and respond to these with appropriate adjustments in physiology. Examples of changes that need to be sensed include illumination, temperature and chemicals in our surroundings in the form of taste and smell. In addition to these specific sensory stimuli, animals respond to relatively ubiquitous elements of the environment such as air and water and the cells and tissues of living creatures need to be able to detect changes in these and tune ongoing cellular function appropriately.

We are all surrounded by air and one of its key constituents is oxygen. Oxygen was discovered in the late eighteenth century by Carl Scheele; it was isolated by Joseph Priestley and Antoine Lavoisier who also named it 'oxygen'. Oxygen forms 20.9% of air and is essential for animal life due to its role in the biochemical reactions that convert nutrients into energy within cells. Oxygen is made available to cells through air inhaled into the respiratory system from where it is absorbed into the bloodstream. Here it is bound to haemoglobin in red blood cells and transported via circulation to the tissues of the body where it dissociates, enters into cells and is used in the biochemical reactions of cellular respiration. In some tissues such as muscle, oxygen is also stored bound to myoglobin.

Given its critical role in cellular biochemistry, animals have evolved multiple mechanisms to ensure that their cells and tissues have adequate amounts of oxygen available. At the level of the whole animal, this is most evident in the well-recognized phenomenon of animals breathing heavily during intense exercise, an effort to enhance the supply of air and thus oxygen to their lungs. These are key mechanisms to ensure adequate blood flow to and oxygenation of tissues and the importance of these discoveries was recognized by the award of a Nobel Prize in Physiology or Medicine to Corneille Heymans in 1938.

In addition to these immediate mechanisms, chronic deprivation of oxygen, for example, by living at high altitudes, has long been recognized to result in adaptive changes in animals. The Nobel Prize in Physiology or Medicine for 2019 has been awarded for discoveries on the mechanisms by which animals cells respond to changes in oxygen levels. The prize has been awarded to Gregg Semenza (Johns Hopkins University School of

William G. Kaelin Jr  Sir Peter J. Ratcliffe  Gregg L. Semenza

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Medicine, USA), William Kaelin Jr (Harvard University, USA) and Peter Ratcliffe (Francis Crick Institute, UK).

Their discoveries have origins in the work of the French physiologist Peter Bert who in the late 19th century demonstrated that an important element of the hypoxia response is an increased production of red blood cells. Increases in red blood cell production are mediated by the hormone erythropoietin (EPO) and consequently enhance the amount of haemoglobin available to carry oxygen to tissues. The sensing of lower partial pressure of oxygen by kidney cells leads to the production of EPO and prior work had shown that increases in EPO production were dependent on an enhanced transcription of this gene. Early work therefore focused on the identification of DNA sequences that might control EPO expression and led to the identification of a 3′ enhancer. This enhancer showed sensitivity to hypoxia in a range of cell types, not just the cells of the kidney. In the 1990s, Gregg Semenza identified, purified and cloned, a transcription factor that regulates these oxygen-dependent responses by binding to the 3′ enhancer of the EPO gene. He named this factor hypoxia inducible factor (HIF). HIF functions as a heterodimer and discrete domains of its $\alpha$ subunit are themselves able to confer oxygen sensitivity to other transcription factors. Thus, oxygen sensing is converted into a transcriptional response by HIF-mediated transcription.

Though the HIF-$\alpha$ transcription factor was initially identified in the context of the transcriptional control of EPO gene, modern methods of pan-genomic analysis suggest that HIF-$\alpha$ regulates more than 500 genes in animal cells. It also interacts with the micro RNA system and has been proposed to also have non-transcriptional mechanisms of action. The consequences of the expression of these target genes lead to numerous adjustments in biochemistry such as the rewiring of cellular respiration from an aerobic to anaerobic mode.

How is oxygen itself sensed in tissues? The answer to this question came from the analysis of the van Hippel Lindau tumour suppressor (pVHL). The work of William Kaelin, Jr who was studying the pVHL gene led to the discovery that pVHL is a E3 ubiquitin ligase that ubiquitinates HIF-$\alpha$. Peter Ratcliffe demonstrated an association between pVHL and HIF-1$\alpha$, and found that pVHL regulates the oxygen sensitive degradation of HIF-1$\alpha$. The Kaelin and Ratcliffe groups then simultaneously showed that the biochemical signal for the ubiquitination of HIF-1$\alpha$ by pVHL is the prolyl hydroxylation of HIF-1$\alpha$, a covalent modification that is itself dependent on oxygen. The enzyme that carries out this hydroxylation was identified as a prolyl hydroxylase (PHD), initially in *C. elegans* and subsequently in mammals. This enzyme is a member of the family of dioxygenases that have an absolute requirement for molecular oxygen as substrate, suggesting that these proteins may be the long sought-after oxygen sensor. Although 2-oxoglutarate oxygenases (of which PHD is member) are widely distributed (there are more than 50 genes in the human genome) in both eukaryotes and prokaryotes and bacteria are known to respond transcriptionally to changes in oxygen levels, the HIF-$\alpha$/pVHL/PHD system appears to be specific to and universal within the animal kingdom. Collectively, these findings have led to our understanding of the core mechanisms by which animal cells sense and respond to oxygen (Figure 1).

Hypoxia in animal tissues occurs in several physiological conditions including living at high-altitude and deep-sea environments. At a practical level the response of the human body to high-altitude hypoxia has been used to enhance athletic performance through training at high altitudes. On the other hand, enhanced oxygen levels have been used in the management of premature babies in neonatology. Hypoxia is also part of a number of key medical disorders. For example, in chronic obstructive pulmonary diseases where the partial pressure of oxygen in tissues is lowered, the constituent cells will need to respond and adapt. It is also well-recognized that as tumours grow, they develop certain regions that are hypoxic due to various factors such as reduced blood flow. Presumably these hypoxic zones undergo adaptive changes mediated by the transcriptional program of the HIF system. Interestingly, Otto Warburg, the German physician and physiologist, who described the oxidation reactions in cellular metabolism (and was awarded a Nobel Prize in 1931 for this work) also reported the eponymous 'Warburg effect' that notes the ability of tumours to grow in the absence of oxygen. The various mechanisms underlying the Warburg effect remain unclear, but often include cellular adaptations to hypoxia through the HIF system. Our understanding of the cellular responses to hypoxia via the HIF system will help decipher the rewiring of metabolism in human tissues under conditions where hypoxia is induced, due to reduced tissue oxygenation resulting from respiratory or circulatory disorders. Given this, there is considerable excitement in targeting the HIF system for novel drugs and therapeutics to manage these conditions.

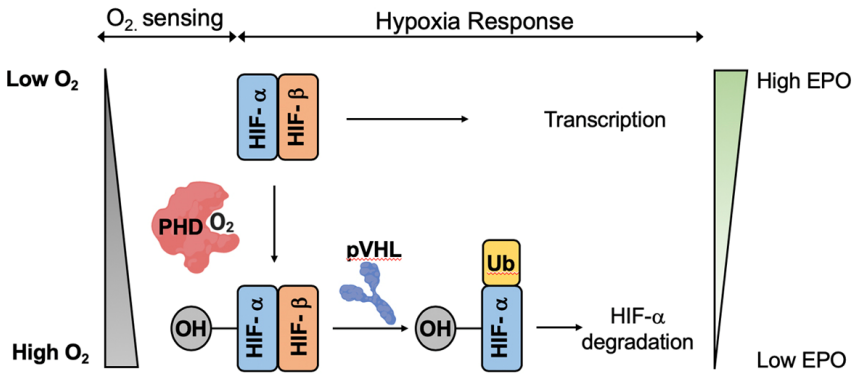


**Figure 1.** Essential elements of the hypoxic response in animal cells: the $O_2$ sensing and hypoxia response modules are depicted. Core proteins involved in the process are depicted: PHD, prolyl hydroxylase; HIF-$\alpha$, hypoxia inducible factor $\alpha$ subunit; HIF-$\beta$, hypoxia inducible factor $\beta$ subunit; pVHL, von Hippel Lindau protein; Ub, ubiquitin. Hydroxylation indicated by –OH. EPO, erythropoietin.

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