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EDITORIAL

Oxygen sensing decoded: a Nobel concept in biology

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Abstract
Oxygen is essential to most organisms as it is a necessity for aerobic metabolism and energy production. Too much or too little oxygen can be deadly, such that mechanisms for fast and titrated response to changing oxygen levels are crucial. These mechanisms have evolved from the studies of *Gregg L. Semenza, William G. Kaelin* and *Peter J. Ratcliffe*. It is through the work of their three laboratories, performed in the 1990s, that the cellular oxygen sensing mechanisms have been decoded. Their discoveries have had major impact for innovation in medicine, especially in the field of angiogenesis research, where oxygen sensing and its consequences have led to enhanced insight in vascular development and strategies for combating angiogenic diseases. On October 7, the Nobel Assembly in Stockholm announced at the Karolinska Institute that the Nobel Prize for Medicine 2019 is jointly awarded to these three scientists for their seminal discoveries on how cells sense and respond to oxygen.

Keywords Oxygen sensing · Angiogenesis · Erythropoietin · Hypoxia Inducible Factor (HIF) · Nobel prize · Vasculature

The element oxygen was discovered in the eighteenth century by *Joseph Priestly* and *Karl Wilhelm Scheele,* and possibly by others, who discovered that oxygen (which they called fire air) was important for combustion and burning of materials. The presence of oxygen in the atmosphere is the result of photosynthesis by living organisms, mainly the marine cyanobacteria. Roughly one-fifth of outside air is oxygen, and living organisms have adapted to its availability. When access to oxygen changes, cells have to react to it, as too low or too high oxygen pressure presents major challenges. At high altitudes, where air contains less oxygen, the secretion of the hormone erythropoietin by the kidneys is stimulated, resulting in the production of more red blood cells, thereby alleviating the shortage of oxygen. Without trying to be exhaustive, the sequence of discoveries leading to the delineation of oxygen sensing mechanisms is as follows. Gregg Semenza and his team were investigating the mechanism behind the enhanced production of erythropoietin (EPO) and found a protein that they called hypoxia inducible factor (HIF), which binds at a site in the EPO gene enhancer that is required for hypoxic activation of transcription [1]. Later, HIF was identified as a complex of HIF-1α and aryl hydrocarbon receptor nuclear translocator (ARNT or HIF-1β) [2, 3]. Thus, HIF acts as a transcription factor for EPO, regulating its mRNA transcript expression. Subsequently, Semenza and also Peter Ratcliffe and his team discovered that the gene for EPO is not the only one that is sensitive to oxygen pressure. Many genes were found to be regulated by oxygen, among which was vascular endothelial cell growth factor (VEGF) [4]. VEGF is a central driving force in the formation of new vasculature, which in turn increases oxygenation, and so VEGF expression is exquisitely adapted to oxygen levels [5]. All of these studies demonstrated that HIF is a universal oxygen sensor that can rapidly induce cells to cope with oxygen shortage. Bill Kaelin and his colleagues discovered the mechanisms at play under normal oxygen: HIF is rapidly degraded to shut off low oxygen-responsive genes. They were investigating a hereditary type of cancer, called Von Hippel–Lindau (VHL) syndrome. This disease is characterized by mutations in the VHL gene, a tumor suppressor gene [6, 7], and the formation

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of tumors throughout the body, often in the kidneys. These tumors were observed to be heavily vascularized and expression of HIF and VEGF, often also EPO, was high in these tumors [8]. Kaelin and his team hypothesized a defect in the oxygen sensing system of VHL tumor cells, which led to the discovery of the regulation of HIF by VHL protein [9, 10]. While under normal conditions VHL protein forms a complex that is involved in degradation of HIF through the protostome [10], mutations in the VHL gene prevent its normal function, resulting in high HIF expression even in the presence of high oxygen levels. This results in unlimited expression of HIF target genes, including VEGF, which in the latter case contributes to excessive angiogenesis.

The three 2019 Nobel Prize in Medicine recipients opened an entire field with far-reaching implications by discovering how low oxygen stabilizes HIF so that it can activate transcription of VEGF-A and other critical genes. For many, their work has been instrumental for enhanced insight into settings of pathological angiogenesis, such as in atherosclerosis [11], rheumatoid arthritis as well as in the fields of ophthalmology (age-related macular degeneration) [12], gynecology (endometriosis and adenomyosis) [13] and cancer. In particular for cancer, dozens of drugs have been developed to inhibit angiogenesis, either directly or indirectly targeting oxygen sensing molecules [14, 15] or by targeting angiogenesis by other mechanisms [16, 17].

We are indebted to the exceptional work of Gregg L. Semenza, William G. Kaelin and Peter J. Ratcliffe. We congratulate them with the Nobel Prize for Medicine 2019.

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