Oxygen Sensing: “Hydroxy” Translates “Oxy”

Roland H. Wenger¹,² and Christian Bauer²

¹Physiologische Institut, Medizinische Universität zu Lübeck, D-23538 Lübeck, Germany; and ²Physiologisches Institut der Universität Zurich CH-8057 Zurich, Switzerland

Have you ever experienced hypoxia? You have, whenever jogging or biking for example, when your heart or your skeletal or respiratory muscles did not receive enough oxygen to cope with the work. In such circumstances, vasodilating substances such as nitric oxide and angiogenic factors such as vascular endothelial growth factor (VEGF) are released and cause increased blood flow and sprouting of new capillaries. In other, more pathophysiological situations such as anemia or lung disease, hypoxia results in increased production of the hormone erythropoietin, which in turn stimulates production of red blood cells that carry oxygen. In all of these circumstances, lack of oxygen elicits adaptive mechanisms that alleviate the potentially damaging effects of hypoxia by increasing vascular diameter, capillary density, blood oxygen capacity, and cellular glycolysis.

As a long-sought “oxygen sensor”, the fact that hemoglobin is the biochemical equivalent of such an intracellular “oxygen electrode” is a heme protein. Their hypothesis was based on the observation that the effects of hypoxia could be inhibited by carbon monoxide and mimicked by transition metals such as cobalt and by reagents that chelate iron. Despite this convincing evidence, the exact molecular nature of the “oxygen sensor” remained undefined until recently, when two groups of investigators around P. J. Ratcliffe and W. G. Kaelin Jr. independently reported that an enzyme with prolyl hydroxylase activity could be the missing link in oxygen sensing.

Two enzymes have now been identified as being of special interest. All précis to Trendsetters are by invitation only.

Prolyl hydroxylases are dioxygenases that require ferrous iron and 2-oxoglutarate as cofactors. They are well known researchers in the field of collagen biochemistry as enzymes that attach an oxygen atom, such as a hydroxyl group, to C-4 of proline. A particular feature of this hydroxylation reaction is the need for a reducing agent, such as ascorbate, to keep the iron atom in the ferrous state. With regard to the target of HIF-α, such a reaction is not simply a “metabolic joke” because both groups of investigators have shown that the highly conserved proline 564 in the ODD domain of HIF-α is hydroxylated only under normoxic conditions and in the presence of sufficient amounts of reduced iron. Binding of HIF-α by pVHL was demonstrated to be strictly dependent on this metabolic labeling of HIF-α. Conversely, decreasing the oxygen availability or chasing the iron with cobalt greatly reduces the interaction of HIF-α with pVHL.

Can this enzyme, named HIF-α prolyl hydroxylase (HIF-PH),
now be regarded as the winner in the race for the discovery of the oxygen sensor? Not quite, but the likelihood is fairly good because this distinct biochemical entity fulfills an impressive number of criteria that were set out for qualification as an oxygen sensor (6). Now we need to identify and clone this enzyme to learn more about its physiological oxygen profile, its cellular regulation in different tissues, and its potential interaction with other redox-sensitive enzymes. However, we should not forget that, apart from protein stabilization, other oxygen-dependent modifications of HIF-α have been suggested to be necessary for its full activity. With this in mind, we look forward to more exciting insights in the field of oxygen homeostasis.

References