Comparative biology of oxygen-sensing in plants and animals

Michael J. Holdsworth and Daniel J. Gibbs

School of Biosciences, University of Nottingham, Loughborough, LE12 5RD, UK
School of Biosciences, University of Birmingham, Edgbaston, B15 2TT, UK

Abstract:
Aerobic respiration is essential to almost all eukaryotes and sensing oxygen is a key determinant of survival. Analogous but mechanistically different oxygen-sensing pathways were adopted in plants and metazoan animals, that include ubiquitin-mediated degradation of transcription factors and direct sensing via non-heme iron(Fe^{2+})-dependent-dioxygenases. Key roles for oxygen-sensing have been identified in both groups, with downstream signalling focussed on regulated gene transcription and chromatin modification to control development and stress responses. Components of sensing systems are promising targets for human therapeutic intervention and developing stress resilient crops. Here we review current knowledge about the origins, commonalities and differences between oxygen-sensing in plants and animals.

Introduction:

Molecular oxygen (O_2) is necessary for many core biochemical pathways and most importantly as the final electron acceptor in mitochondrial electron transport, and is therefore essential to the vast majority of eukaryotes. Oxygen first appeared in quantity on earth as a result of the evolution of oxygenic photosynthesis at least 2.3 Ga (billion years ago) (reviewed in [1]) (Figure 1). Subsequently as part of the evolution of endosymbiosis with an ancient cyanobacterial group before 1 Ga early eukaryotic algae gained the ability to photosynthesise, leading to further increases in O_2 levels that peaked at over 30% during the Carboniferous (~360 to 300 Ma). Endosymbiosis with purple non-sulphur bacteria (that became mitochondria), that predated chloroplast endosymbiosis, may have allowed early eukaryotes to tolerate O_2 and use the energy of mitochondrial aerobic respiration to become multicellular. Various hypotheses have been advanced that increased O_2 levels were either highly poisonous and catastrophic for early anaerobic eukaryotes or that these organisms were already pre-adapted to deal with reactive oxygen species that aided evolution of O_2 tolerance (discussed in [2]).

Oxygen varies in the environment (for example declining with increased altitude, or as a result of submergence in water or under the soil surface) and also internally during development or disease [3, 4]. It is clear that for such an essential component of intracellular

biochemistry, sensing and response to changing O_2 levels must be an important feature of multicellular eukaryotes. In this review we focus on biochemical pathways that evolved in plants and animals to sense and respond to reduced O_2 levels (hypoxia). Analogous pathways evolved in both lineages, that target nuclear-located processes for response. We highlight the different evolutionary trajectories of pathways, the importance of dioxygenases as conserved sensors of hypoxia, the physiological importance of oxygen-sensing and avenues for identification of novel sensors and pathway components.

The ubiquitin proteasome system as a hub for oxygen-sensing across kingdoms

In metazoans and angiosperms major mechanisms directing changes in gene expression under hypoxia are controlled by hypoxia-responsive transcription factors. Their stability is intrinsically linked to O_2 levels and in oxygenated environments they are polyubiquitylated and rapidly degraded by the 26S proteasome (Figure 2). In metazoans, the Hypoxia Inducible Factor (HIF, also known as EPAS) heterodimer consists of HIFα and β bHLH-PAS domain subunits (Figure 2). Three HIFα proteins are found in mammals; HIF1α and HIF2α contain N- and C-terminal transactivation domains (NTAD and CTAD), whilst HIF3α lacks the latter [4]. The NTAD of HIFα contains conserved proly residues that are hydroxylated using O_2 by proly 4-hydroxlases (PHD, also known as EGLN) [5, 6]. This modification then permits binding of the E3 ubiquitin ligase von Hippel-Lindau protein (pVHL) to initiate polyubiquitylation [7, 8], leading to HIFα degradation. Hypoxia limits PHD activity, precluding pVHL binding, thus allowing association with HIFβ and re-localisation to the nucleus [4] (Figure 2). The CTAD-containing HIFα variants can also be hydroxylated on asparaginyl residues by Factor Inhibiting HIF1α (FIH), which limits HIFα association with transcriptional co-factors [9]. This separate O_2-triggered modification also therefore contributes to inhibition of HIF activity through a parallel hydroxylation-dependent but non-proteasomal route.

In flowering plants, the group VII ETHYLENE RESPONSE FACTOR transcription factors (ERFVIIs) control anaerobic gene expression under hypoxia [10]. Following co-translational Methionine excision, in high O_2 levels the N-terminal Cysteine of ERFVIIs is converted to Cys-sulfinic acid by PLANT CYSTEINE OXIDASEs (PCOs), which leads to amino-terminal (Nt)-arginylation by ATE [11, 12]. Nt-Arg-ERFVIIs are then targeted for proteasomal degradation by the E3 ligase PROTEOLYSIS (PRT)6 [13, 14]. This pathway also requires nitric oxide (NO) [15]. Thus, similarly to HIFα regulation, coupling protein turnover to O_2 availability results in ERFVII stabilisation under hypoxia (Figure 2). Recently, a mammalian protein with high similarity to PCO, cysteamine (2-aminoethanethiol) dioxygenase (ADO), was characterised and shown to control O_2-dependent turnover of non-nuclear REGULATOR OF G PROTEIN SIGNALLING (RGS) 4,5,16 proteins via the mammalian Arg/N-degron pathway

[16]. This highlights an alternative mechanism for O_2-sensitive proteolysis in mammals, equivalent to the predominant system in plants.

There is evidence that alternative pathways can also target HIFα and ERFVIIs for degradation, revealing additional proteolytic mechanisms for fine-tuning their stability [4, 17-20]. Furthermore, animal PHD and plant PCO enzymes also have non-HIF and -ERFVII targets, respectively. In *Arabidopsis thaliana*, the PCO targets LITTLE ZIPPER (ZPR)2 and Polycomb Repressive Complex (PRC)2 component VERNALIZATION (VRN)2 are subject to ubiquitin-mediated degradation [21, 22], whereas hydroxylation of candidate non-canonical PHD/FIH substrates, such as IKKβ, p53, and OTUB1, can have different effects on protein activity and interactions [23].

The key role of non-heme iron(Fe^{2+})-dependent dioxygenases in oxygen-sensing

The enzymes catalysing both prolyl-/asparaginyl-hydroxylation (PHD, FIH) and Nt-cysteine oxidation (PCO, ADO) belong to the non-heme iron(Fe^{2+})-dependent dioxygenase family, so called because their catalytic sites contain a redox active iron directly coordinated to the protein, and incorporate both atoms from O_2 into substrates [24]. PHDs function as physiological O_2 sensors due to their high K_mO_2 values, which for the dominant PHD2 isoform (dependent on the length of peptide studied) has variably been reported from less than 100μM to 1700 μM, much higher than *in vivo* O_2 concentrations [25, 26]. In contrast, FIH has a higher affinity for O_2 than PHDs, indicating that greater decreases in O_2 availability would be required before its activity is inhibited [27]. PHD/FIH incorporate one oxygen atom into the target HIFα prolyl or asparaginyl residue, whilst the second decarboxylates 2-oxo-glutarate (2-OG) to produce CO_2 and succinate [23, 28] (Figure 2). PCOs and ADO also have high K_mO_2 values above typical plant and animal tissue O_2 concentrations, but in contrast to PHDs they are not 2-OG dependent, they integrate both atoms directly into Nt-Cys to generate Cys-sulfinic acid [12, 16, 29].

Metazoans encode multiple PHD isoforms, which are differentially expressed and have varying subcellular localisations, although the main mammalian PHD2 variant is cytosolic and constitutively expressed [4, 30]. Flowering plant PCOs have different sensitivities to O_2 and pH, and divergent substrate preferences based on assessment of their activities on peptide sequences [29]. Of the five PCOs in *A. thaliana*, PCO4 is the most catalytically potent suggesting that it may be the dominant variant. Apparently without an active oxygen-transport system, strong gradients of hypoxia exist in plant tissues (obvious examples include tubers and seeds) [3, 31] and it may be that PCOs with different affinities for O_2 operate in different tissues/at different developmental time points. Interestingly, a subset of these oxygen-sensing enzymes in animals and plants are transcriptionally induced by low- O_2 levels, suggesting that

homeostatic mechanisms for dampening the hypoxic response have evolved in both kingdoms [4, 11].

In addition to PHD and PCO/ADO proteins, there are many other non-heme iron(Fe^{2+})-dependent dioxygenases in animals and plants [24, 32], although several of these, including collagen prolyl hydroxylases and certain JmjC (Jumonji C) domain lysine demethylases (KDMs), are unlikely to sense physiological changes due to their high O_2 affinities [23, 33]. Nonetheless, it was recently shown that some histone-specific KDMs (KDM5A and 6A) do have K_mO_2 values in the requisite range for sensing intracellular O_2, and are able to directly modulate the methylation status of chromatin dependent on O_2 availability [33, 34] (Figure 2). Under hypoxic conditions, KDM activity is reduced, resulting in enhanced global levels of histone methylation, regulating gene expression and cell fate. The activity of a separate non-histone KDM (KDM3A), which is involved in the demethylation of the transcriptional co-activator PGC-1α, also connects O_2 availability to the regulation of genes linked to mitochondrial biogenesis [35], suggesting others await discovery.

Evolutionary origins of the different oxygen sensing systems

Components of the Arg/N-degron pathway are conserved in eukaryotes, though distinct evolutionary trajectories are observed. Whereas ATE activity is highly conserved across all major groups, E3 ligase functions for recognising distinct destabilising residues (carried out by UBR-type proteins in non-plants) were split early in plant evolution [36] (Figure 1). ERFVIIs are not present in the genome of basal land-plants *Physcomitrella patens* or *Marchantia polymorpha*, and VRN2 and ZPR2 appeared with angiosperms [21, 22]. As the nature of Nt-Cys oxidation was for several years obscure, a major advance was the identification of the PCOs in *A. thaliana* [11]. This showed that Nt-Cys oxidation required PCO enzyme activity, and genetic removal of *PCO* function leads to ERFVII stabilisation and enhanced hypoxia tolerance. The identification of ADO indicates that oxygen-sensing via this pathway is ancient, predating the split between animal and plant groups (>1 Ga) [16] (Figure 1), and may indicate that a major mechanism of oxygen-sensing in early eukaryotes was through cysteine dioxygenase control of Nt-Cys oxidation, during periods of earth history with comparatively low O_2 levels. Alternatively, it may suggest that originally the major function of the pathway was NO sensing, and became coupled to O_2 as atmospheric levels rose. PCO-type Nt-cysteine dioxygenases have not been found in fungi, that diverged from animals after plants, indicating loss of the capacity of this group to oxidise Nt-Cys and use this pathway for oxygen-sensing [16]. Genes encoding Met-Cys initiating RGS proteins are only present in vertebrate genomes, and those encoding IL-32 only in mammalian lineages (Figure 1).

Although the PCO/ADO branch of the N-degron pathways is ancient in eukaryotes, the HIF pathway is only present in metazoan animals (choanoflagellates, closest extant relatives

to animals, do not contain bHLH-PAS domain proteins, [37]) (Figure 1). A functioning HIF system was identified in the placozoan *Trichoplax adhaerens*, representing one of the simplest multicellular animals [38]. A recent analysis of representatives of basal metazoa groups porifera (sponges) and ctenophores failed to identify pVHL or PHD-like proteins, or hypoxia-regulated gene expression [37]. One feature of the evolution of the HIF system appears to be increased diversification of components in derived evolutionary groups. Whereas *T. adhaerens* contains single proteins for each component of the pathway mammals contain multiple variants of HIFα and PHD [38]. The appearance and diversification of a functional HIF pathway, that correlates with large increases in atmospheric and oceanic O_2, may have influenced the concomitant explosion of animal diversity and size beginning around the Cambrian period (~540 Ma) (Figure 1).

Integration of oxygen-sensing with downstream signalling and physiology

Key observations related to major consequences of oxygen-sensing have been the identification of nuclear changes in response to hypoxia. In both plants and animals these converge on transcription of hypoxia-related genes and chromatin structure. In plants an evolutionarily-conserved core set of hypoxia-related genes are activated by ERFVIIs in response to hypoxia-induced stabilisation, through a conserved Hypoxia Responsive Promoter Element (HRPE) [10]. Similarly, animal Hypoxia Response Elements (HREs) are bound by HIF factors to enhance low O_2 responsiveness [39]. Low O_2 levels also influence chromatin structure, through the stabilisation of components of chromatin modifying complexes (VRN2 as part of PRC2 [21]), via enhanced expression of chromatin modifiers (gene activation by HIF [40]), or directly through repression of histone H3 demethylation activity of KDMs [33, 34]. In both animal and plant responses, genes encoding biochemical pathways associated with enhanced tolerance of hypoxia are important targets (including fermentative metabolism, glycolysis and an inhibition of mitochondrial oxidative phosphorylation), and the control of pathways with oxygen-requiring reactions or that occur in hypoxic niches are also important [22, 41, 42]. Two animal cytoplasmic substrates of ADO have been identified, RGS4,5,16 and INTERLEUKIN (IL)-32 [16, 43], that gives the possibility of more rapid response to declining O_2 than transcriptional circuits, since their immediate stabilisation would trigger a change more quickly than responses dependent on increased protein production through HIF control of gene expression. Both IL-32 and RGS4/5 are transcriptional targets of HIF, indicating a possible interaction between the two sensing systems [16]. Moving forward it will be important to decipher the comparative timescales through which PHD/FIH, KDM and ADO activity leads to cellular changes, as this likely contributes to physiologically relevant fine tuning of the overall hypoxia response.

Analyses of physiological functions reveal the broad reach of oxygen-sensing systems, and specific roles are related to the different lifestyles of plants and animals. As plants are sessile a key function of oxygen-sensing is related to perception of waterlogging and flooding [13, 14]. Both stabilised ERFVIIs and VRN2 enhance survival of hypoxia [13, 14, 21]. It was recently shown that the plant Cys-initiating substrate ZPR2 is stabilised by the hypoxic environment of the shoot apical meristem, regulating the production of new leaves [22], and VRN2 also accumulates in hypoxic meristems, where it modulates flowering time and root development [44]. In addition, hypoxia-enhanced stability of ERFVIIs was shown to repress chlorophyll synthesis (an O_2-requiring pathway) in dark grown seedlings [41], as well as lateral root development [45].

The HIF pathway plays major roles in O_2-homeostasis, including erythropoiesis (development of red blood cells) and angiogenesis (development of new blood vessels) (reviewed in [46]). Similar to ZPR2/VRN2 in plant meristems, HIF1α is stabilised within hypoxic hematopoietic stem cells (that give rise to blood cells) [42]. Stabilised HIF1/2α enhance expression of growth regulators (erythropoietin (EPO) and angiogenic growth factors) and associated components (for example systems for iron uptake and utilisation [46]). An important role of the HIF system is in adaptation of animals to high altitude, where the partial pressure of O_2 is reduced. Genome wide association studies identified allele signatures in human populations associated with life at high altitudes in the Tibetan Plateau (average altitude 4000 m, pO_2 13 kPa) for both HIF2α and PHD2. For example, in modern Tibetan populations a variant of *EGLN1*/*PHD2* (Asp4Glu; Cys127Ser) was shown to have a lower K_mO_2 suggesting that it promotes increased degradation of HIF at high altitude (lower pO_2) thus reducing HIF levels to those equivalent to low altitudes [47]. Interestingly one allele of *EPAS1*/*HIF2A* enriched in Tibetan populations appears to have been derived from ancient hominid Denisovans [48]. Many studies demonstrate wider roles for the HIF system, indicating that oxygen-sensing by this pathway influences many aspects of cellular biochemistry, growth and development (discussed in [49]).

Since the PCO/ADO pathway also acts as an NO sensor [15, 43], the stability of both animal and plant substrates also regulates responses to intracellular NO levels that accompany internal and external stress. For example, destruction of RGS proteins to induce cardiomyocyte proliferation can also be induced by endothelium-derived NO [50]. Stabilisation of ERFVIIs by reduced NO enhances hypoxia tolerance and tolerance to other abiotic stresses (including high salinity) [51, 52]. It is still unclear exactly where NO acts within the pathway. Although an in vitro reconstituted mammalian system was shown to be NO dependent [43], in vitro activity of PCO/ADO on peptides does not require NO [16, 29]. It is possible therefore that NO influences the activities of enzyme components of the pathway in vivo (ATE, PCO/ADO or UBR1/PRT6), and it was shown that PRT6 contains an NO binding domain [53].

Factors other than hypoxia can influence oxygen-sensing pathways. A sub-pool of ERFVIIs is stable and sequestered at the plasma membrane through association with ACYL CoA BINDING PROTEINs (ACBP) during normoxia [14, 54]. Zinc excess in the soil (detrimental to plant growth), inhibits PCO enzymes thus causing stabilisation of ERFVIIs [55]. Non-canonical mechanisms also control HIF stability; for example, increases in succinate during the progression of certain types of cancer can allosterically inhibit PHD activity to trigger HIF accumulation under normoxia [56, 57]. The possible mechanisms influencing O_2-responsive factors, and therefore the breadth of possible affected physiological processes will be much wider than those specifically related to O_2 or NO.

Pathologies and interventions of oxygen-sensing in plants and animals

Oxygen-sensing pathways represent key cellular targets for counteracting diseases and enhancing stress resilience. HIF signalling controls a range of cellular responses, and also drives tumorigenesis and the maintenance of tumour microenvironment in certain cancers [58]. Thus, interventions that impact the HIF pathway have the capacity to treat pathologies associated with these processes. *EPO*, a target of HIF, is down-regulated in patients with chronic kidney disease (CKD) due to reduced O_2 consumption [59]. Several PHD inhibitor molecules (PHIs) have been developed that stimulate increased EPO production in CKD patients to counteract renal anaemia [60], acting as 2-OG mimetics or iron-chelators to inhibit enzymatic activity and increase HIF stability in normoxia [59]. Chemicals that disrupt other aspects of HIF signalling have also been identified as potent repressors of cancer progression [61]. For example, cancers in patients with VHL disease result from ectopic accumulation of HIF2α [58], and a novel drug that specifically disrupts the HIF2α/HIF2β dimer to downregulate HIF2 signalling was recently shown to limit tumour progression [62]. The development of inhibitory molecules that target discrete HIF or PHD isoforms, as well as other regulatory points in the HIF signalling pathway, will help to increase therapeutic specificity and efficacy of such treatments.

Genetic manipulation of O_2-signalling components in crop species can increase resistance to waterlogging-induced hypoxia, as shown in barley through genetic reduction in *HvPRT6* expression/activity [63], whilst ERFVIIs provide increased tolerance to multiple abiotic stresses [52] and biotic stresses where pathogen-associated hypoxia is an integral factor [64-66]. In rice (*Oryza sativa*), the ERFVII SUB1A-1 is a major regulator of submergence tolerance that has been bred into high yielding varieties [67]. SUB1A-1 is naturally uncoupled from O_2-dependent degradation despite containing Cys2 and downstream Lys residues [13, 68] suggesting that the plant oxygen-sensing system has been targeted by natural selection for adaptation in wetland environments, and that biotechnological approaches could be used to achieve similar outcomes in flooding-susceptible crops.

Conclusions and unresolved questions

Where to look for undiscovered oxygen-sensors? Based on structures and domains of already identified proteins there are clear candidates to test as novel components of oxygen-sensing pathways. Plant and animal genomes contain Jumonji C domain-containing KDMs in addition to those already shown to act as oxygen-sensors. Determining those with a physiologically relevant (high) K_mO_2 would be a first step in defining potential roles as sensors. Although plants do not contain HIFα-like sequences, both plants and animals contain hundreds of proteins initiating Met-Cys, that could be substrates of PCO/ADO action, in addition to endopeptidase substrates cleaved to reveal Nt-Cys. Cys2 is evolutionarily constrained in most eukaryote proteomes [69] suggesting that this is an important determinant related to O_2/NO-sensing. In addition, recently it was hypothesised that mechanisms other than PCO-regulated destabilisation may act to promote oxygen-sensing in plants, in several cases backed-up by experimental data [70].

Why is N-degron mediated oxygen-sensing not the primary system in metazoans as it is in angiosperms? The HIF system evolved only in one lineage of animals, whereas the PCO/ADO pathway evolved early in eukaryotes (Figure 1). Perhaps the unavoidable link of the PCO/ADO pathway to a requirement for NO made this pathway unsuitable, or possibly it was not suitable for large mobile organisms. Lack of transcriptional response to hypoxia in the marine sponge *Tethya wilhelma* indicates that the PCO/ADO pathway does not perform this function in basal animals, though complete anoxia did result in large changes in gene expression [37]. It is unclear what advantage the coupling of NO- and oxygen-sensing in this pathway has; it may be a remnant of evolutionary drivers early in eukaryote history, where O_2 levels were low, which might also suggest early Nt-cysteine dioxygensases had high affinities for O_2, making the pathway primarily important for responding to changes in levels of intracellular NO.

There are several striking commonalities in the major oxygen-sensing systems of angiosperms and metazoans. Both require dioxygenases with O_2-sensitivity within a physiological range, both directly target nuclear-factors for UPS-mediated destruction, and both result in large changes in gene expression with downstream physiological consequences providing homeostatic control of O_2 response. An important goal of future research will be to define the links between O_2 affinity of pathway dioxygenases and their expression patterns, allowing an understanding of how these enzymes sense all physiologically possible internal O_2 tensions. The complete gamut of influenced processes and interactions is yet to be resolved, at the intracellular level there are clearly similarities of interactions between oxygen-sensing pathways and mitochondrial function (key for oxidative phosphorylation), well

understood for the HIF system, but requiring more understanding for the PCO/ADO pathway in animals and plants. It is likely that many components of known oxygen-sensing pathways remain to be discovered, including dioxygenases with novel activities, and PHD/ADO/PCO targets. An important goal of future research will be to investigate the use of these components to enhance tolerance to hypoxia for both medical and agricultural interventions.

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Glossary of abbreviations:

ACBP	Acyl-CoA-binding domain-containing protein
ADO	cysteamine (2-aminoethanethiol) dioxygenase
ATE	ARGINYL TRANSFERASE
bHLH	basiv Helix Loop Helix DNA binding domain
CKD	Chronic Kidney Disease
EPAS	Endothelial PAS domain-containing protein
EPO	Erythropoietin
ERFVII	Group VII ETHYLENE RESPONSE FACTOR
FIH	Factor Inhibiting HIF1α
HIF	Hypoxia Inducible Factor
HRE	Hypoxia Response Element
HRPE	Hypoxia Responsive Promoter Element
IKKβ	Inhibitor of nuclear factor kappa-B kinase subunit beta
KDM	JmjC (Jumonji C) domain lysine demethylase
NO	Nitric oxide
Nt-	Amino terminus of the protein
NTAD/CTAD	N- and C-terminal transactivation domains of HIF
OTUB1	Ovarian tumor domain containing ubiquitin aldehyde binding protein 1
PAS	Per-Arnt-Sim domain
PCO	PLANT (Nt-)CYSTEINE OXIDASE
PHD(EGLN)	proly 4-hydroxlases/ Egl nine homolog
PHI	PHD inhibitor molecule
PRC2	Polycomb Repressive Complex 2
PRT6	PROTEOLYSIS6 E3 ligase N-recognin
pVHL	von Hippel-Lindau protein E3 ligase
RGS	REGULATOR OF G PROTEIN SIGNALLING
SUB1A	SUMERGENCE1A
UBR	Ubiquitin protein ligase E3 component N-recognin
VRN2	VERNALIZATION2
ZPR2	LITTLE ZIPPER2

Figure 1:

Evolutionary history of core components of the HIF and PCO/ADO oxygen-sensing pathways.

Ages of key evolutionary events, and predicted O_2 levels at distinct ages of earth history are indicated (Billion years ago; Ga). GOE, Great Oxidation Event, first appearance of significant atmospheric O_2 levels. Possible times of appearance of oxygen-sensing pathway components (ovals with gene name indicated) are shown based on presence of similar protein sequences or functional testing in extant taxonomic groups, and important functional diversification indicated. Animal-specific components are in greys, plant-specific in greens.

Figure 2:

A comparison of major oxygen-sensing systems in metazoans and flowering plants.

Mammalian HIFα and plant ERFVII transcription factors are stable under hypoxia where they drive hypoxic gene expression through binding to genes bearing specific promoter elements (HRE, HRPE). In oxygenated environments, prolyl residues in HIFα are hydroxylated by 2-OG dependent PHD dioxygenases prior to ubiquitylation (Ub) by the pVHL E3 ubiquitin ligase, whilst the N-terminal Cys of ERFVIIs is converted to Cys-sulfinic acid by 2-OG-independent PCO dioxygenases, prior to ATE-mediated arginylation that permits recognition by the PRT6 E3 ubiquitin ligase. ZPR2 stability is also regulated via PCO in plants to control shoot meristem function. The recently discovered ADO pathway in mammals is equivalent to the PCO pathway in plants and regulates the stability of non-nuclear RSG and IL-32 substrates that do not directly modulate gene expression. Mammals and angiosperms have contrasting oxygen-regulated mechanisms controlling histone modifications. In humans, KDM dioxygenases demethylate histones in high O_2, but are inhibited under hypoxia; KDMs are also found in plants, but their oxygen-sensitivity is yet to be established. In plants, stability of the VRN2 subunit of PRC2, a major histone methylating complex, is regulated via PCOs similarly to ERFVIIs. Acronyms and proteins names are defined in the main text and glossary. Hatched blue box highlights the conserved N-degron-based O_2 sensing pathways in mammals and plants.

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