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Anoxia

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Synonyms

Extreme hypoxia and anoxia have been used interchangeably; Severe hypoxia; The terminology hypoxia

Definition

Literal Definition

Anoxia literally means the complete absence of oxygen (O_2) and has been described as the state where no O_2 (0 % O_2) is detected in the tissue. This definition contrasts the definition of hypoxia, which means low levels of oxygen as opposed to complete absence.

Conceptual Definition

The major function of the vasculature is to deliver oxygen and nutrients to cells and remove carbon dioxide and other metabolic by-products from them. Oxygenated blood is distributed in each tissue according to the functions and needs of that tissue, which differs from one tissue to another. Therefore, when studying different tissues and cell types, there are significant variations in cellular response(s) based on oxygen level and/or corresponding nutrient level. Hence, oxygen tension has to be viewed with respect to a particular tissue/organ and is therefore essentially a functional definition, because there are marked normal differences in oxygen tension in the body. For example, normal physiological oxygen level in the superficial skin region is 1.1 %, whereas in subpapillary plexus it is 4.6 % and in intestinal tissue it is 7.6 % oxygen. Thus, a decrease in the normal O_2 for a tissue or organ, sufficient to induce a molecular or physiological response, would be an operational definition with respect to a specific tissue/organ.

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Several studies have shown that when cancer cells are exposed to hypoxia (defined as 1 %, 0.5 %, or 0.1 % oxygen in those studies) versus anoxia (defined as $O_2 < 0.5$ %, 0.1 %, or 0.001 % in various studies), distinct pathways are switched on in anoxia that are either absent or switched on in much lower levels in hypoxia. Hence, anoxia has been referred to lack of oxygen that triggers cellular and molecular responses that differ to the response in hypoxia. These differences in response of cells to hypoxia versus anoxia have been correlated to cell-fate differences, respectively. Cellular fates during oxygen deprivation are diverse, including death, survival, continued proliferation, quiescence (or hibernation/dormancy), senescence, and differentiation. Such diverse fates depend on the severity and/or duration of oxygen/nutrient deprivation and the genetic background of the cell type. Therefore, the distinction of terminology between hypoxia and anoxia is important because in hypoxia, cells have a much better chance to adapt and survive compared to anoxia. Therefore, anoxia can also be defined with respect to cell fates that differ to the fates observed in hypoxia. Whereas cells can continue to grow in hypoxia for some time, anoxia on the other hand can redirect cell fate toward hibernation/dormancy or death. These key cell-fate differences in hypoxia versus anoxia are due to the key pathways induced, epigenetic changes, and metabolic switches. Indeed, experiments performed with *Caenorhabditis elegans* have demonstrated that sensing anoxia is a separate pathway to sensing and adapting to hypoxia, where organisms survive anoxia via undergoing suspended animation.

Characteristics

Oxygen is absolutely essential for life, so the molecular mechanisms underlying responses to low levels of oxygen are central to the cell. The cell has to be able to sense and interpret the level of oxygen present in its environment, and based on this interpretation, the cell will make a decision (termed cellular decision-making) for a particular fate such as death versus survival. For example, when cells are exposed to hypoxia, such as during intensive exercise, information flow within the cell interprets the oxygen level as being "hypoxia" (low), which in turn results in anaerobic metabolism that enables the cell to produce energy and survive under anaerobic conditions. This adaptive response can be viewed as a normal physiological process, which is primarily modulated via the hypoxia-inducible factor 1 (HIF1) pathway [see entry on "► Hypoxia"]. In contrast, fate of cells in a pathological setting will be different than the aforementioned physiological condition of exercise. Several diseases such as ischemic heart disease, stroke, and cancer are associated with oxygen and nutrient deprivation. In ischemic conditions such as in the heart or brain, cells initially respond by adapting and surviving via switching on anaerobic metabolism. As ischemic conditions become severe, cells receive no oxygen or nutrients (notably glucose) and eventually die but can also hibernate and survive. This scenario is similar in solid tumors, which are known to contain regions of hypoxia and anoxia. Tumor cells may survive anoxia due to diminished apoptotic pathways, genetic mutations, protein mislocalization, as well as via dormancy-mediated survival.

In Vitro Creation of Hypoxia and Anoxia

Several units have been used to describe the amount of oxygen present in the experimental atmosphere. It has been proposed that the partial pressure of oxygen should be given in the SI unit kilopascal (kPa, 1000 N per m^2) in line with international agreements. 1 kPa equals 10 bar or 7.5 torr (or mmHg where 760 mmHg equals 100 % O_2). In gas mixtures containing 10,000 ppm (parts per million) of oxygen, the partial pressure is 1 kPa. Most reports have used the unit mmHg or % O_2 to refer to the amount of oxygen present in experimental atmosphere. The use of ambient air has been referred to the "normal oxygen tension" (normal levels of oxygen) often termed normoxia or 21 % oxygen. Normoxia is used as means of experimental control, to which hypoxia is compared to. Typically, experiments testing the effects of hypoxia tend to culture cells in incubators with a gas mix of 5 %

CO_2 and 95 % N_2 until the desired level of hypoxia is reached. The hypoxic cells are then compared to cells cultured in normoxia, which consist of ambient air and 5 % CO_2.

Anoxia has been achieved in vitro by using incubators with an atmosphere of 5 % CO_2, 90 % N_2, and 5 % H_2 and a palladium catalyst to scavenge traces of oxygen. Alternatively, a continuous flow of 95 % N_2 and 5 % CO_2 has been used. Such conditions have achieved O_2 levels lower than 0.1 % and even 0.001 % O_2 in tissue cultures of moderate to low cell density, and therefore anoxia has been addressed as O_2 levels <0.1 % or 0.001 % in several publications.

In vitro normoxia, defined as 21 % O_2 (160 mmHg, pO_2), is at least four times higher than the physiological in vivo normoxia in most arterial beds. Therefore, it has been proposed to make in vivo conditions the standard against which in vitro values should be measured. In venous blood, there is an average 5.3 % O_2 (or 40 mmHg O_2), and while some tissues have higher than average oxygen levels, in some tissues (and especially solid tumors) oxygen levels are lower than the average. Twenty-one percent O_2 is not physiological, especially for tumors where oxygen levels of around 1 % (5–10 mmHg) can be a borderline between well- and poorly oxygenated tumors. Thus, normally oxygenated (>10 mmHg or 1 % O_2) tumors are mostly hypoxic compared to in vitro conditions of 21 % O_2 and express HIF1, indicating that many tumors live under hypoxia. The in vitro conditions of hypoxia and anoxia coincide well with oxygen measurements performed with polarographic O_2 electrode needles on patient tumors, which have demonstrated extremely low levels of oxygen such as <2.5 mmHg (<0.3 % O_2), including 0 mmHg (0 % O_2), termed anoxia.

Causes and Consequences of Tumor Anoxia

Areas of low oxygen in tumors may be a consequence of several mechanisms such as abnormal tumor vasculature, limited tissue perfusion, and tumor-associated or therapy-associated ▶ anemia leading to a reduced oxygen transport capacity of the blood. Clinical studies with oxygen electrodes and molecular markers have shown oxygenation patterns in human tumors to be heterogeneous with respect to the severity and duration of exposure to levels of low oxygen, ranging from 10 mmHg to below 2.5 mmHg including 0 mmHg. Two types of tumor hypoxia (which if prolonged or severe will lead to anoxia) can be distinguished: perfusion-limited and diffusion-limited hypoxia. Hypoxia will precede anoxia, and consequently anoxic tissues will have had induction of hypoxic pathways too. Perfusion-limited or acute hypoxia/anoxia is transient and may be a result of severe structural and functional abnormalities of the tumor microvessels. These abnormalities cause disturbance in the blood supply, leading to temporal shutdown of vessels and gradients of oxygen and nutrients (notably glucose) and even reversal of the blood flow. The lack of oxygen can also be caused by an increase in diffusion distances between cells and O_2, resulting in diffusion-limited O_2 supply, leaving cells chronically deprived of oxygen and other nutrients. Over this course of chronic hypoxia and/or anoxia, some cells die, resulting in areas of ▶ necrosis that demarcate regions of hypoxia and anoxia, also termed perinecrotic region. In addition to oxygen deprivation, these regions are also deprived of nutrients, where distinct survival pathways of autophagy and/or dormancy can become activated.

Whereas adaptation to hypoxia is a survival mechanism, anoxia has traditionally been viewed as a death-inducing condition and recognized by some as a protective mechanism to prevent possible cellular transformation associated with anoxic cellular damage. However, it should be noted that anoxia and/or glucose deprivation could also result in activation of survival pathways and mechanisms such as autophagy and dormancy/hibernation. Control of both gene expression and protein localization during oxygen and nutrient deprivation, including epigenetic mechanisms, is emerging as an important cellular response, which can result in dormancy-mediated survival. In addition to dormancy-mediated survival, tumor cells can additionally escape death, attributed to defects in several death pathways, such as mutations in the p53

pathway. Escaping death via dormancy could result in selection of cells, which can result in recurrence giving rise to a more aggressive and therapy-resistant phenotype.

Information Flow Within the Cell

The environment of the cell contains information and the cell has to be able to recognize this information and interpret it. One way in which cells recognize and interpret information (such as anoxia) is via intracellular protein localization and translocation. In cancer, intracellular proteins are often mislocalized, and therefore information (be it anoxia or any other extracellular information) is misinterpreted. Whereas the interpretation of information as being hypoxia results in an adaptive response, the interpretation of information as being anoxia could be achieved by altered protein localization, which results in fates such as hibernation-mediated survival or death. For example, in hypoxia, the factor termed HIGD1A is mitochondrial, whereas in severely anoxic tumor regions, or severe ischemic regions created after anti-angiogenesis treatment, HIGD1A also accumulates in the nucleus. Although the nuclear function of HIGD1A remains unknown, HIGD1A has been associated to metabolic stress-induced dormancy. Hence, the definition of anoxia may also be related to altered and or specific intracellular protein localization and cell fate.

Cell Fate in Anoxia

Under the tissue culture of normoxia, the transcription factor HIF1α is unstable, degraded, and virtually undetectable. As soon as cells experience hypoxia (usually evident at 5 % oxygen), HIF1α is rapidly stabilized and induced (see "► Hypoxia" entry), regulating majority of the adaptive/survival genes such as glycolytic enzymes and ► VEGF. HIF1α is also induced by anoxia, but several reports have shown that prolonged anoxia results in downregulation of HIF1α in vitro. This in vitro finding has also been observed in some human tumors, which lack of HIF1α expression in perinecrotic anoxic regions, potentially due to lack of glucose, which is needed for HIF1α stability.

Anoxia-Induced Dormancy

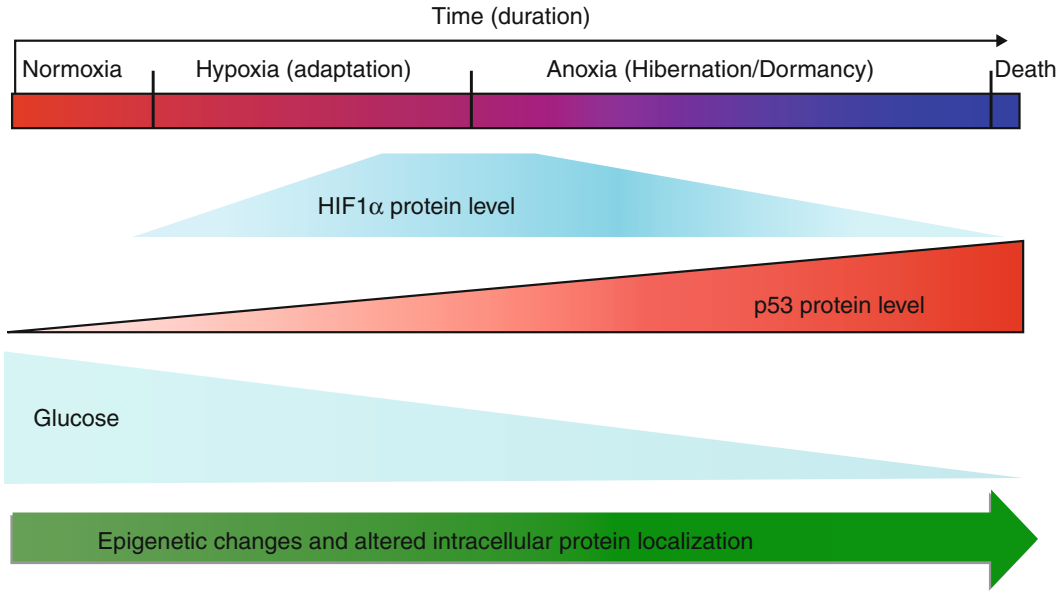
In general, when tissues become ischemic, they are subjected to both oxygen and nutrient deprivation. Anoxic tumor regions are also commonly deprived of nutrients, notably glucose (Fig. 1). One way that cells can survive such metabolic stress is via lowering cellular ROS and oxygen consumption, which are parameters associated with quiescence and dormancy-mediated survival. Ironically, recently it has been suggested that hypoxia-regulated genes are not induced in hypoxia but can be induced in anoxic regions in vivo that are severely ischemic and putatively lack glucose. The induction of hypoxia-regulated factors such as HIGD1A or AMPK may modulate oxygen consumption and cellular ROS to induce dormancy-mediated survival, which is not desired in growth permissive hypoxic conditions. Epigenetic mechanisms modulated by ► DNA methyl transferases (DNMTs) may dictate expression of dormancy-regulating genes in anoxia, hence inducing dormancy, but prevent their expression in hypoxia, thus permitting growth. Therefore, cells can use epigenetic mechanisms as one way to discriminate between hypoxia and anoxia, directing their fate toward growth versus hibernation, respectively. From this point of view, the definition of anoxia may be correlated to epigenetic mechanisms and specific pathways that are activated to induce dormancy versus proliferation pathways that are induced in hypoxia.

Interplay Between HIF1α and p53 Determining Cell Fate in Anoxia

Several factors such as apoptosis-inducing factor (AIF) or GAPDH can have cell survival and/or cell death functions attributed to their diverse subcellular localization. Another factor that can be localized to the mitochondria, cytoplasm, or nucleus is p53, which can trigger apoptosis to eliminate damaged cells, or it can induce cell-cycle arrest to enable cells to cope with stress and survive.

p53 and Cell Death

p53 is expressed at low levels in unstressed cells due to degradation by the ► proteasome. Upon



Anoxia, Fig. 1 Proposed model (Adapted from Schmid et al. 2004) showing the relation of HIF1α and p53 level in hypoxia and anoxia. Hypoxic activation of HIF1α is attenuated when p53 starts to accumulate. With progressing time under anoxia, p53 accumulates further and promotes HIF1α destruction. Cell survival versus apoptosis is one distinction between extreme end points of hypoxia and anoxia. In vivo, anoxia is commonly associated with nutrient deprivation, notably glucose. Epigenetic changes toward anoxia have indicated a correlation to dormancy

exposure to extremely low levels of oxygen, termed severe hypoxia, p53 is stabilized and becomes active. Accumulation of p53 in severe hypoxia/anoxia has been shown to both inhibit the HIF1α transcriptional activity and reduce the HIF1α protein levels, which might explain why some reports have observed HIF1α levels to decline under prolonged anoxia. This scenario might have implications for cell fate in anoxia. In hypoxia, transactivation of HIF1α could serve to protect cells enabling adaptation and survival. In anoxia, the inhibition and destruction of HIF1α via p53 may result in a switch from an adaptive hypoxic response into an anoxic death response. This HIF1α-p53 interactive pathway is one potential mechanism that could determine cellular fate of death when hypoxia and anoxia need to be discriminated by the cell. This cellular fate of hypoxia versus anoxia can become deregulated in cancer. Tumor cells defective in p53 can escape the anoxic death and endure longer periods of anoxia, resulting in selection of more aggressive cancer cells.

p53 and Cell Survival

p53 may also contribute to survival. In general, when tissues become ischemic, they are subjected to both oxygen and nutrient deprivation. Anoxic regions are commonly also deprived of nutrients, notably glucose (Fig. 1), that can result in an increase of cellular ROS and induce death. Recently it has been shown that oncogenic HrasV12-expressing MEFs with wild-type p53 survive better than their *p53* null counterparts upon glucose starvation attributed to increased oxidative phosphorylation. This pro-survival effect is partly due to positive regulation of the cellular energy supply by p53. However, severe prolonged hypoxia (72 h 0.5 % O_2) coupled with glucose starvation results in severe cell death in both cell types. It should be noted, however, that wild-type p53 cells still significantly survive better than *p53* null counterparts in such severe in vitro ischemic conditions. At this time it is not clear whether this survival is due to cell-cycle arrest-mediated dormancy, although p53 can regulate lipid metabolism to restrain proliferation. This phenomenon may be necessary to maintain cells in a dormant state and important

for surviving anoxic glucose-deprived tumor regions. Additionally, to maintain survival of dormant cells in the absence of nutrients, p53 may modulate usage of alternative nutrient sources such as increased fatty acid oxidation as an alternative energy source to glycolysis or regulate glutaminolysis, where glutamine can be eventually converted to α-ketoglutarate for use in the tricarboxylic acid cycle to produce ATP.

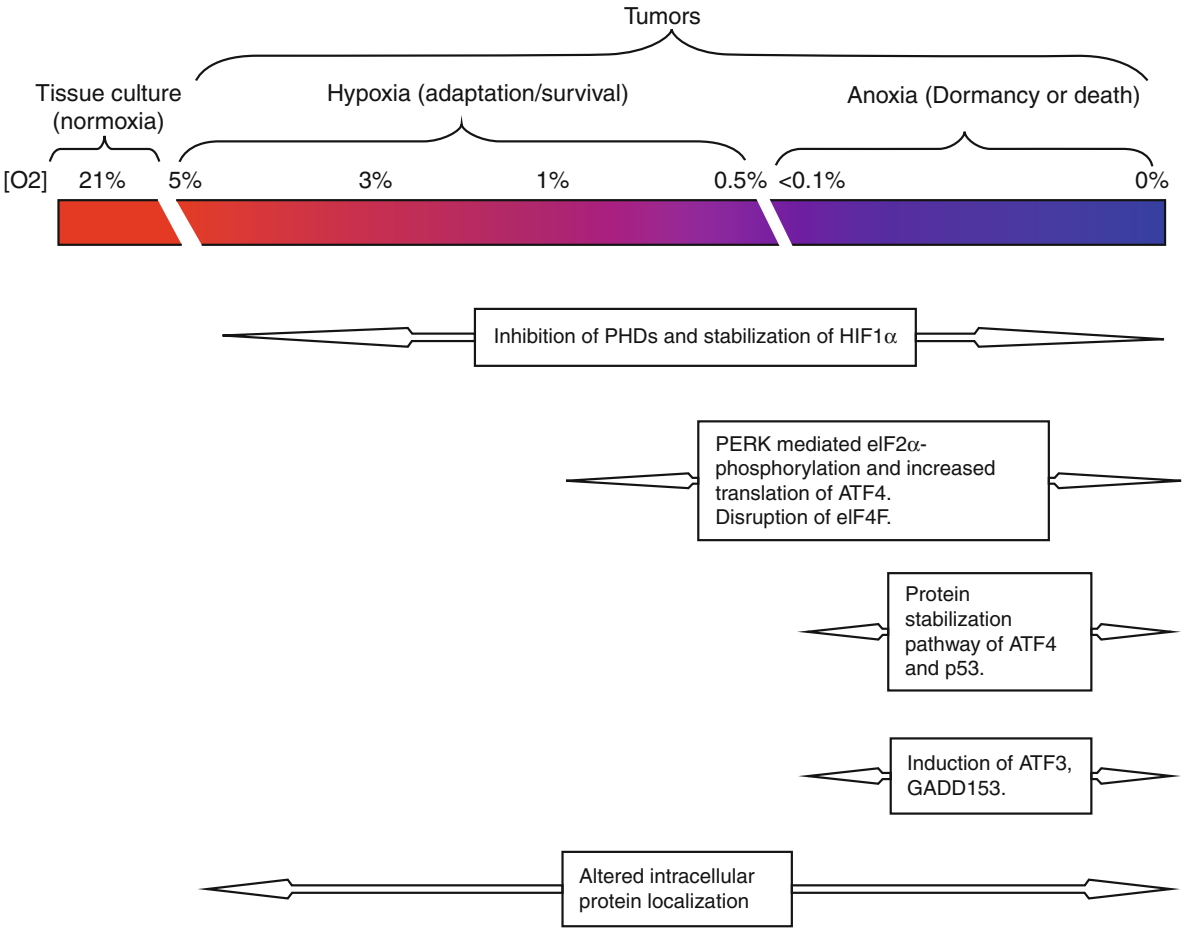
To summarize, in anoxia, p53 can dictate cell fate toward both death and survival, potentially dependent on its localization and or/mislocalization (nuclear versus mitochondria) and other parameters such as nutrient level. Figures 1, 2, and 3 summarize pathways and cell fates in various oxygen levels.

Oxygen Sensing/Signaling Pathways Specific to Anoxia

Several distinct oxygen sensing/signaling pathways have been discovered that together determine the cellular response to hypoxia and anoxia. The best characterization of these is a transcriptional response initiated by oxygen-dependent stabilization of HIF1α in hypoxia and anoxia. The stability of HIF1α and its transcriptional activity are regulated by oxygen-dependent hydroxylation of specific amino acid residues. Hydroxylation at two prolyl residues (Pro 402 and Pro 564 in human HIF1α) enables interaction of HIF1α with the von Hippel-Lindau protein (pVHL) that targets HIF1α to proteasomal degradation. These hydroxylations are catalyzed by a series of three closely related HIF prolyl hydroxylases, known as orthologs of *C. elegans* EGL-9, designated as PH (prolyl hydroxylase) domain containing enzymes (PHD), i.e., prolyl hydroxylases (PHD1, PHD2, PHD3). The transcriptional activity of HIF1α is controlled by hydroxylation of an asparaginyl residue (Asn-803 in human HIF1α), catalyzed by a HIF asparaginyl hydroxylase, also termed factor inhibiting HIF (FIH). Hydroxylation at this site blocks transcriptional activation. The HIF hydroxylases all iron (II) and two oxoglutarate-dependent dioxygenases that have an absolute requirement for molecular oxygen. In hypoxia and anoxia, therefore, hydroxylation is reduced, which allows HIF1α to accumulate by escaping proteasomal degradation. The PHDs could be considered as O_2 sensors of the hypoxia and anoxia HIF1α pathway (Figs. 2 and 3).

Anoxia results in the induction of several factors including the ATF/CREB (activating transcription factor/cyclic AMP response element-binding protein), the family of basic region-leucine zipper (bZip), the transcription factors such as ATF3 and ATF4, the CCAAT/enhancer-binding protein (C/EBP) transcription factor family member GADD153, and the transcription factor XBP1. Such anoxic response is independent of HIF1α and is mediated by the ▶ unfolded protein response (UPR), which activates the PERK kinase, IRE1 and ATF6, and takes place after the hypoxic HIF response. The signaling from downstream effectors of IRE1, PERK, and ATF6 merges in the nucleus to activate transcription of UPR target genes.

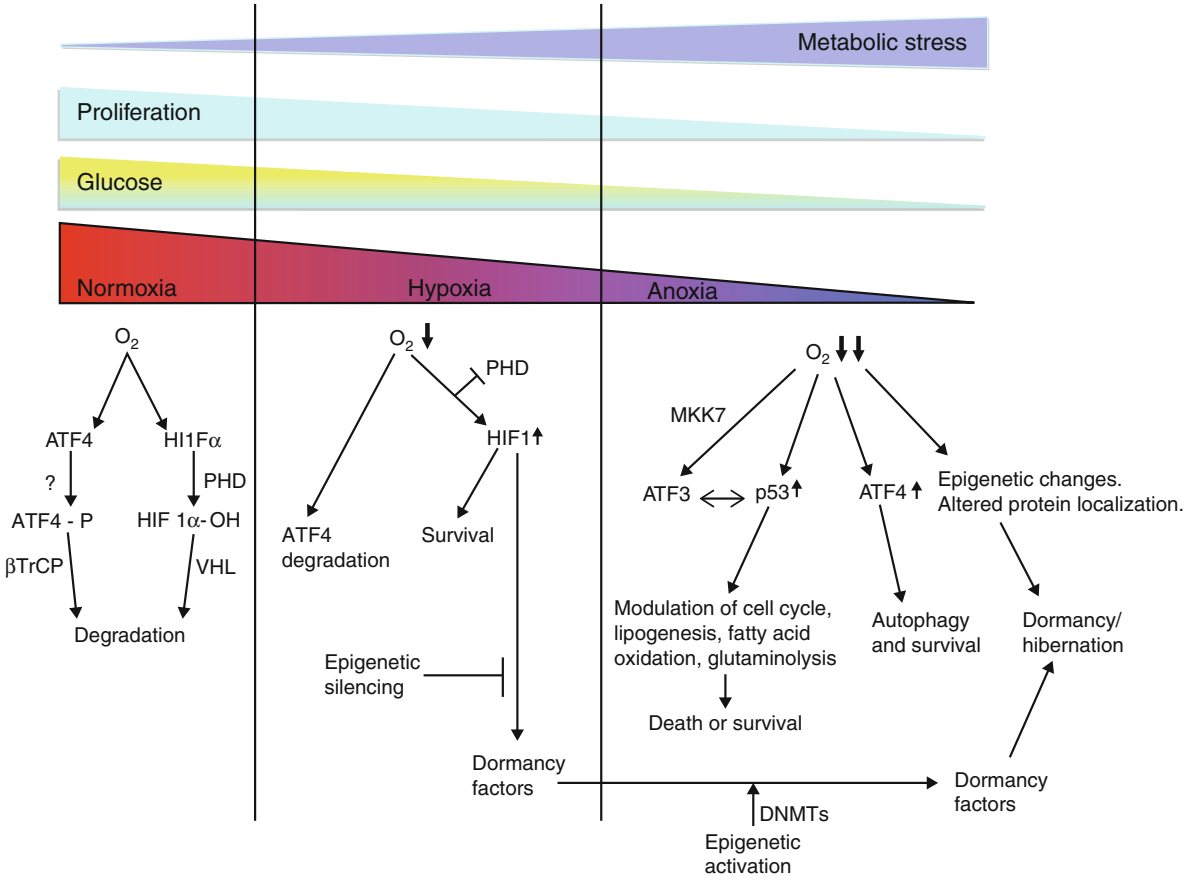
The regulation of mRNA translation has emerged as an important mediator of the cellular response to hypoxia and anoxia. Distinct mechanisms of translational control have shown to discriminate between initial and prolonged conditions of in vitro generated anoxia. Anoxia results in inhibition of global mRNA translation, which is a biphasic response. A central mediator of the initial translational response to anoxia is the phosphorylation of the eukaryotic initiation factor 2α (eIF2α) by PERK protein kinase. The phosphorylation of eIF2α in anoxia is extremely rapid, whereas under hypoxia eIF2α is phosphorylated to a smaller degree and requires prolonged hypoxic exposure. Cells can also distinguish between initial and prolonged anoxia by eliciting a biphasic inhibition of translation. The first phase is due to transient eIF2α phosphorylation, and the second phase of translation inhibition correlates with disruption of the cap-binding complex eIF4F. The initial anoxic response of translational inhibition may be important during acute anoxia in tumors, which could be important for enduring anoxia. Although the phosphorylation of eIF2α results in global translational reduction, it specifically induces/increases the translation of ATF4 mRNA, subsequently increasing ATF4 protein levels, which is



Anoxia, Fig. 2 Oxygenated tumors are mostly hypoxic compared to in vitro conditions of 21 % O_2 and express HIF1α over a broad range of oxygen level, which is sensed primarily by PHDs. Secondary responses, after the induction of HIF1α in hypoxia, include translational control and protein stabilization pathways, which are more specific to sensing anoxia, rather than hypoxia, and can result in induction of factors such as ATF3, ATF4, and GADD153. Information flow within the cell differs between hypoxia and anoxia. Altered intracellular protein localization can enable the cell to interpret this information

important for anoxia survival. Indeed, acute anoxic stress (2 h) has shown to be capable of eliciting a cytoprotective pathway, improving the survival of transformed cells following prolonged anoxic stress (24 h), resulting in the clonogenic outgrowth of a population of adapted cells.

Another important mediator of the cellular response to anoxia may be protein stabilization pathways. HIF1α is stabilized and induced rapidly at hypoxic conditions of 5 % O_2. Upon reoxygenation it is rapidly degraded. In contrast to HIF1α, the transcription factor ATF4 is not induced by such hypoxic conditions, but is induced by anoxia (Figs. 2 and 3). Like HIF1α, ATF4 protein is unstable and degraded in the presence of oxygen. Therefore, modulation of protein degradation pathways seems to be part of a sensing mechanism of both hypoxia and anoxia, but whereas the PHD pathway of HIF1α degradation is blocked in hypoxia, hypoxic degradation of ATF4 is still active. The exact mechanism of ATF4 stabilization in anoxia remains unclear, but under normal oxygen levels of tissue culture, ATF4 is degraded by two mechanisms: (i) ATF4 stability modulated by the $SCF^{\beta TrCP}$ class of ubiquitin ligase and (ii) ATF4 stability modulated by the histone acetyltransferase p300 (HAT p300). ATF4 contains the ▶ βTrCP recognition motif DSGXX(X)S, and when the serine of



Anoxia, Fig. 3 Diagram of specific pathways that could discriminate between hypoxia and anoxia. Whereas both HIF1α and ATF4 are degraded in normoxia, only HIF1α is induced in hypoxia, whereas ATF4 and p53 are mostly induced in anoxia. In all cases, different protein degradation pathways are involved. Which kinase phosphorylates ATF4 with subsequent recognition by βTrCP targeting ATF4 to proteasomal degradation remains unknown and is shown as ?. One way in which cells may survive anoxia is via dormancy. Epigenetic mechanisms via DNMTs and/or p53 may determine survival, dormancy, or death. In vivo, oxygen deprivation is often accompanied by metabolic stress due to nutrition (notably glucose) deprivation. This metabolic stress can determine the response of cells to oxygen deprivation and should be taken into account when performing in vitro experiments

this motif is phosphorylated, it results in interaction with βTrCP and subsequent degradation by the proteasome. Histone acetyltransferase p300 induces ATF4 stabilization by inhibiting ATF4/β TrCP interaction and subsequent degradation. How this relates to anoxic stabilization of ATF4 remains unclear (Fig. 3). Other mediators of the cellular response to anoxia include the mRNA stability pathways and the ▶ MAPK pathway. The transcription factor ATF3 has been shown to be induced by anoxia. PHDs have been suggested to be potentially involved in regulation of ATF3 induction in anoxia, but a precise role remains unclear. ATF3 mRNA has been shown to be more stable in anoxia compared to normoxia, and translation of ATF3 is also increased in anoxia in a PERK-dependent manner. Induction of ATF3 in MKK7 knockout primary mouse embryonic fibroblasts is fully blocked, which has suggested that the MKK7 pathway might be part of mediating the induction of ATF3 in anoxia. Thus, multiple pathways can converge into regulating ATF3 in anoxia. Interestingly ATF3 can inhibit but also stabilize p53 contributing to cell fate in anoxia (Fig. 3). Figures 2 and 3 summarize some key pathways and factors in various oxygen levels.

Therapeutic Implications of Anoxia

Hypoxia and anoxia are known to directly or indirectly confer resistance to X- and gamma radiation and some chemotherapies leading to treatment failures. Many classical radiobiological studies have shown that anoxic cells (O_2 below 0.5 mmHg) are maximally resistant to the lethal effects of irradiation. Therefore, both hypoxia and anoxia are therapeutic problems.

Factors that are induced by anoxia, such as ATF3 and ATF4, have shown to be potentially involved in tubulogenesis, induction of VEGF and ▶ angiogenesis, cell survival, and metastasis. In response to anoxia, protein synthesis is decreased by 60–70 % within 1 h and remains significantly repressed for up to 24 h but is completely reversible upon reoxygenation. Hence, in anoxia some cells might survive, be selected for, and continue to grow upon reoxygenation. Indeed, cells that lack downstream targets of PERK (e.g., ATF4) and IRE1 (e.g., XBP1) have shown to be sensitive to anoxia compared to wt cells that contain ATF4 or XBP1. Such anoxic survival is not entirely dependent on HIF1, and cells that are deficient in HIF1 are not more sensitive to anoxia compared to wt cells that contain HIF1. Thus, downstream targets of PERK and IRE1 are important for surviving and adapting to anoxia, as apposed to hypoxia where HIF1 mediates the major survival pathway. Targeting HIF1 alone might select for more aggressive cells with an intact anoxic response pathway.

In addition to hypoxia, anoxia might confer a total separate drug resistance pathway to hypoxia. For example, overexpression of the anoxic factor ATF4 has shown to result in multidrug resistance, and hence, cells under anoxia that induce ATF4 may become selected for a treatment resistance phenotype, if only the hypoxia cascade of HIF1α is targeted.

In contrast to hypoxia, anoxia may select for a dormant therapy-resistant phenotype that may contribute to tumor recurrence years after therapy. Therefore, understanding the complex definition of anoxia in an ischemic setting where nutrients are also lacking will lead to more specific targeted therapies in the future.

Cross-References

- ▶ Angiogenesis
- ▶ Hypoxia-Inducible Factor 1
- ▶ Necrosis
- ▶ Oxygenation of Tumors
- ▶ Reactive Oxygen Species
- ▶ Unfolded Protein Response and Cancer
- ▶ Vascular Endothelial Growth Factor

Glossary

Anemia Below normal levels of red blood cells or hemoglobin, or both.

Angiogenesis The process of developing new blood vessels.

βTrCP Beta-transducin repeat-containing proteins (βTrCP) serve as the substrate recognition subunits for the SCF complexes. βTrCP interact with substrates phosphorylated within the DSGXX(X)S destruction motifs. SCF-β-TrCP-mediate ubiquitination and proteasomal degradation of phosphorylated substrates.

DNA methyl transferases These are enzymes that transfer a methyl group from S-adenosyl-L-methionine to the carbon 5 position of cytosine.

MAPK Mitogen-activated protein kinases (MAPK) are important intermediates in signal transduction pathways that are initiated by many types of cell surface receptors. MAP kinase cascades are organized by a core-signaling module consisting of three protein kinases: a MAP kinase kinase kinase (MKKK), a MAP kinase kinase (MKK), and a MAP kinase.

Necrosis The sum of the morphological changes indicative of cell death and caused by the progressive degradative action of enzymes. It may affect groups of cells or part of a structure or an organ.

Proteasome Protein degradation machinery within the cell that can digest a variety of proteins. The proteasome is itself made up of proteins and requires ATP to work.

ROS Reactive oxygen species. These are chemically reactive molecules containing oxygen that are formed in biological systems as by-products of the reduction of molecular oxygen. ROS include the superoxide radical anion, hydroxyl radical, hydrogen peroxide, hydroperoxyl radical, singlet oxygen, and peroxyl radical.

VEGF Vascular endothelial growth factor (VEGF) is a factor made by cells that stimulates the formation of new blood vessels, a process called angiogenesis. VEGF also acts as a mitogen for vascular endothelial (vessel lining) cells, stimulating these cells to divide and multiply.

XBP1 X-box binding protein 1 (XBP1) is transcription factor and a transcriptional activator of the UPR. Splicing of XBP1 mRNA is initiated by the RNAse activity of IRE1 to generate mature XBP1 mRNA.

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