

# Hypoxia

Subjects: **Oncology**

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Hypoxia is a condition commonly observed in the core of solid tumors. The hypoxia-inducible factors (HIF) act as hypoxia sensors that orchestrate a coordinated response increasing the pro-survival and pro-invasive phenotype of cancer cells, and determine a broad metabolic rewiring. These events favor tumor progression and chemoresistance. The increase in glucose and amino acid uptake, glycolytic flux, and lactate production; the alterations in glutamine metabolism, tricarboxylic acid cycle, and oxidative phosphorylation; the high levels of mitochondrial reactive oxygen species; the modulation of both fatty acid synthesis and oxidation are hallmarks of the metabolic rewiring induced by hypoxia.

Hypoxia

Chemotherapy

hypoxia-inducible factors

## 1. Introduction

Depending on the tissue type, there is a wide variability in the oxygen ( $O_2$ ) levels, ranging from 9.5% (72.0 mmHg) in kidneys <sup>[1]</sup>, 7.6–6.8% (57.6 mmHg–51.6 mmHg) in gastrointestinal tract <sup>[2][3]</sup>, 5.6% (42.8 mmHg) in lungs <sup>[4]</sup>, 5.4% (40.6 mmHg) in liver <sup>[5]</sup>, and 4.4% (33.8 mmHg) in the brain <sup>[6]</sup>.  $O_2$  levels below these values are considered hypoxic. Physiological hypoxia implies an adaptive and homeostatic response, such as vasodilation and/or up-regulation of hypoxia response genes, to maintain stable levels of  $O_2$ . On the contrary, in pathological hypoxia, the homeostatic mechanisms do not compensate adequately the falling in  $O_2$  levels <sup>[7]</sup>.

The fast rate of growth in solid tumors makes them susceptible to  $O_2$  shortage in poorly vascularized areas and leads to the development of intratumoral hypoxic regions <sup>[8][9]</sup>. Neo-angiogenesis is a compensative response to intratumoral hypoxia. However, the tumor vasculature is composed of leaky vessels with chaotic architecture and easy tendency to collapse under the pressure of growing tumor and stromal cells <sup>[10]</sup>. Although the new vessels formed supply  $O_2$ , the irregular architecture and the vascular collapse reduce the oxygenation in many tumor areas that reach 1–1.3% (8–10 mmHg)  $O_2$  pressure <sup>[7][11][12]</sup>. The cycling between vessels formation and collapse induces fluctuation of  $O_2$  levels, producing repeated cycles of hypoxia and normoxia within specific areas of tumor bulk <sup>[13]</sup>. Moreover, the absence of lymphatic drainage induces intermittent vascular collapse and creates, temporarily and acutely, hypoxic areas that have been proposed to contribute to progression and/or relapse <sup>[14]</sup>. Chemotherapy used in cancer treatment can further damage blood vessels, contributing to generate areas with chronic hypoxia in the tumor mass <sup>[11]</sup>. Microregions with very low (i.e., near to zero) levels of  $O_2$  are heterogeneously distributed within the tumor bulk, with a prevalence of better oxygenated areas, characterized by a high rate of cell division and tumor growth around the capillaries. The newly generated cells often migrate

towards the regions far from vessels <sup>[15]</sup>. Indeed, hypoxia increases the invasive potential of cells by affecting the extracellular matrix (ECM) <sup>[16][17][18]</sup>, e.g., by stimulating the paracrine secretion of soluble factors that generate a fibrotic and stiff ECM, favorable to cell spreading <sup>[19][20]</sup>. Notably, even when re-exposed to O<sub>2</sub>, hypoxic tumors maintain high the expression of hypoxia-sensitive genes inducing metastasis and resistance to oxidative stress <sup>[21]</sup>, conserving a “hypoxic memory” that determines a peculiar aggressiveness <sup>[22]</sup>.

Hypoxia not only affects neoplastic cells, but also implies changes in metabolism and functions of infiltrating cells, such as cancer-associated fibroblasts (CAFs) and tumor-associated macrophages (TAMs). These changes may impair or favor the neoplastic growth, producing cellular quiescence, differentiation, apoptosis, or necrosis, depending on the degree, persistence, and severity of hypoxia. The tolerance to hypoxia, i.e., the ability to enter a quiescent but viable status, determines the persistence of hypoxia-tolerant cells that are aggressive and hard to be eradicated pharmacologically <sup>[23]</sup>.

As a consequence of the different oxygenation, solid tumors are metabolically heterogeneous: better oxygenated regions rely on mitochondrial oxidative phosphorylation (OXPHOS), while hypoxic areas are more dependent on anaerobic metabolism <sup>[21]</sup>. This metabolic reprogramming is coordinated by the hypoxia-inducible factors (HIF) family. According to our present knowledge, up to 2% of the human genome is modulated by HIF transcription factors <sup>[24]</sup>. This review will focus on the metabolic rewiring induced by hypoxia, on the implications of such rewiring in tumor progression and chemoresistance, on the new therapeutic opportunities that may emerge with a deep knowledge of the metabolic reprogramming occurring in hypoxia.

## 2. The Metabolic Rewiring Occurring in Hypoxic Tumors Supports Chemoresistance

The metabolic rewiring in both glycolysis and mitochondria induced by hypoxia cause chemoresistance by cooperating with enhanced pro-survival pathways and reduced apoptosis, EMT activation, increased DNA repair, alterations in drug metabolism, changes in drug targets <sup>[25][26][27]</sup>.

The increased acidification of TME produced by the upregulation of glycolytic enzymes and MCT4 is a first reason of chemoresistance. On the one hand, the low extracellular pH (pHe) favors the protonation of weak bases, such as anthracyclines, followed by their inactivation and sequestrations within lysosomes once entered within the cancer cell, a mechanism known as “ion trapping” <sup>[28][29]</sup>. Second, a typical feature of hypoxic and acidic tumor regions is the increased expression of alkalinizing enzymes. The Na<sup>+</sup>/H<sup>+</sup> exchanger (NHE) is a typical example of transporter that is up-regulated in response to the acidification: the increased intracellular pH (pHi) produced by its activity creates the optimal conditions for Pgp efflux that is maximally efficient at 7.6-7.8 pH <sup>[30]</sup>. Indeed, restoring pHi to 7.4–7.2 by blocking NHE reverses the resistance to doxorubicin, a typical Pgp substrate, in colon cancer cells <sup>[31]</sup>. Other alkalinizing enzymes are the plasma membrane associated CAIX and CAXII that are under the direct transcriptional control of HIF-1α <sup>[32][33]</sup>. CAXII co-localizes with Pgp in several solid tumors <sup>[34]</sup> and in particular in the CSC component <sup>[33]</sup>. Such interaction increases the catalytic activity of Pgp by creating slightly alkaline pH at plasma membrane level <sup>[35]</sup>.

Chemoresistance in hypoxic tumor areas has also been associated with altered mitochondrial metabolism, fusion, fission, and mitophagy [36]. On the one hand, since ABC transporters need a constant supply of ATP, one should expect that hypoxic cells—characterized by lower OXPHOS [37] and higher mitophagy [38]—provide less ATP to ABC transporters, thus, resulting more chemosensitive. Contrarily to these expectations, by up-regulating the Bcl-2/adenovirus E1B 19-kDa interacting protein 3 (BNIP3) [39], an inducer of mitophagy, HIF-1 $\alpha$  induces chemoresistance to 5-fluorouracil [40], gemcitabine [41], and cisplatin [42]. Indeed, mitophagy allows an efficient recovery of ATP, reducing equivalents and building blocks, which support chemoresistance by increasing ABC transporters activity, prevent the chemotherapy-induced oxidative stress and repair macromolecules damaged by chemotherapeutic agents. The production of ROS often associated with an altered OXPHOS in hypoxic tumor regions may induce mtDNA damages that further reduces the efficiency of OXPHOS [43]. However, such defective mitochondrial energy metabolism triggers a compensatory response characterized by the upregulation of PGC-1 $\alpha$  and PGC-1 $\beta$ , which trigger mitobiogenesis. This mechanism has been proved to induce resistance to cisplatin in non-small cell lung cancer with mtDNA mutations that resulted in a 50% reduction of the NADH:ubiquinone oxidoreductase activity [44]. Overall, the mitochondrial-related parameters (lower OXPHOS and ATP production, higher ROS, increased mitophagy, increased mtDNA mutations) that characterize the hypoxic tumor cells induce chemoresistance.

Moreover, cancer cells often have the ability to exploit both glycolysis and OXPHOS, fueled by glutaminolysis and FAO. In this way, cells shift from one energetic pathway to the other one, according to the glucose availability [45]. This metabolic plasticity allows meeting the increasing requirements of energy and building block, necessary to proliferate, migrate, survive, and stimulate neo-angiogenesis in response to stressing agents as chemotherapeutic drugs [46]. Having a constitutively active glycolysis [8], but also an increased rate of FAO [47] and glutaminolysis [48], HIF-1 $\alpha$ -expressing cells exhibit a very high metabolic plasticity that allows a better survival in response to glucose and O<sub>2</sub> shortage, or chemotherapy. We suggest that the pleiotropic effects of hypoxia on metabolic reprogramming all contribute to chemoresistance by different but cooperating mechanisms.

### 3. Conclusions and Future Perspectives

Drug resistance is well known as the primary cause of therapeutic failure in cancer treatment. The mechanisms of chemoresistance involve a combination of cell-intrinsic factors such as oncogenic drivers or mutations, TME-associated factors, pharmacokinetic factors. Hypoxia is a common feature of TME. It plays an important role in selecting cells challenged by a low O<sub>2</sub> supply and forced to rewire their metabolism. This training to survive under unfavorable conditions inevitably make cells more resistant to exogenous stresses such as chemotherapy. HIF-1 $\alpha$ -dependent chemoresistance relies on the transcriptional activation of genes determining cell proliferation, metastasis, EMT, maintenance of stem cell-like properties, drug efflux, and metabolic reprogramming.

The typical metabolic signature of hypoxic tumors is characterized by increased glucose uptake and fermentation into lactate, decreased pHe/increased pHi, reduced TCA cycle and OXPHOS, increased production of mtROS, increased uptake of AAs, and increased synthesis of anti-oxidant metabolites as GSH. All of these features contribute to chemoresistance. The accelerated glycolysis supplies cells with sufficient ATP to promote cell survival

and with glycolysis intermediates for biosynthetic purposes. The increased mitophagy characterizing hypoxic cells sustains the possibility of recovering ATP. The altered pH inactivates several drugs that are active as weak bases, or sequesters them into lysosomes after protonation. The increased production of sub-cytotoxic mtROS, coupled with the higher levels of anti-oxidant metabolites, train cells to be less susceptible to the oxidative damage induced by chemotherapy.

If targeting HIF-1 $\alpha$  could represent an effective approach because it blocks a great number of processes determining chemoresistance, HIF-1 $\alpha$  inhibitors have the disadvantage of huge toxicity, due to the inhibition of physiologically important HIF-1 $\alpha$ -dependent processes, such as ischemia-reperfusion response in non-transformed tissues. Targeting the metabolic pathways controlled by HIF-1 $\alpha$  and re-programming them as in normoxic cells may improve the efficacy of chemotherapeutic drugs and/or attenuate chemoresistance. Although metabolic modifiers have already been tested in clinical trials, side effects deriving from the inhibition of metabolic pathways in non-transformed tissues cannot be excluded. However, the metabolic signature of hypoxic cancer cells—based on high anaerobic glycolysis and low mitochondrial metabolism—is quantitatively different from the normal tissues. This quantitative difference may open a therapeutic window at which metabolic modifiers could be safely used against hypoxic cancer cells, without damaging non-transformed tissues. Nanotechnology-based drug delivery, employing tumor-targeting liposomes or nanoparticles, could aid to increase the delivery and the vectorization of the metabolic modifiers towards the tumor, increasing the therapeutic benefits and reducing the side effects. Finally, some endogenous metabolites, such as pyruvate or melatonin, differentially produced by hypoxic cells and non-tumor tissues, have revealed significant chemosensitizing properties, coupled with lower risks of toxicity.

Thanks to the deep knowledge of the metabolic rewiring induced by hypoxia, and causing chemoresistance, a precision medicine based on specific metabolic modifiers can be proposed as a novel chemosensitizing strategy against aggressive and refractory tumors.

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