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Review Article

Hypoxia Mediated Glycoprotein-170 Expression: Role in Cancer Cells Chemo Resistance

Gabriela Antonio-Andres and Sara Huerta-Yepez*

Hemato-oncological Unit, Children's Hospital of Mexico, Federico Gómez, Mexico

***Corresponding author:** Sara Huerta-Yepez, Hemato-oncological Unit, Children's Hospital of Mexico, Federico Gómez, Mexico

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Abstract

Solid tumors frequently grow in a micro-environment characterized by hypoxia (<2% O_2 tension). This condition, together with the abnormal activation of specific oncogenic pathways, increases the activity of the hypoxia-inducible factor-1α (HIF-1α), a transcription factor that is known to control more than 200 genes involved in multiple cells process including in neo angiogenesis, apoptosis, metabolic rewiring, metastasis and drug resistance. HIF-1α induces the expression of P-gp, protein that acts as an energy-dependent pump to transport cytotoxic agents out of the cells, and its expression is correlated with resistance to multiple drugs in several kinds of cancer. Hypoxia induces chemoresistance via induction of P-gp. In this review, we discuss the multiple and interconnected circuitries that link hypoxic environment and drug resistance focus in the regulation of P-gp. We believe that pharmacological inhibitors of HIF-1α and modulators of P-gp, although characterized by low specificity and anti-cancer efficacy when used as single agents, may be considered as chemosensitizers against hypoxic and chemo refractory tumors in the near future.

Keywords: Hypoxia; HIF-1 alpha; P-gp; Chemo-resistance; Cancer; Gp-170

Introduction

The development of resistance to pharmacological effects in different treatment regimens has been considered one of the main causes of failure to clinical chemotherapy in patients with some type of cancers and consequently the mortality [1]. It has been proposed that tumor hypoxia is associated with resistance to chemotherapy, since highly hypoxic tumor cells cannot proliferate well and dysfunctional vascular supply limits distribution of the drug, leading to initial treatment failure [2]. Beyond this event, some types of cancer that have an optimal response to treatment schemes and then subsequently develop resistance. Resistance can be to a wide spectrum of molecules with structural characteristics and mechanisms of action completely different from each other, resulting in the phenomenon known as multidrug resistance (MDR) [3]. One of the most investigated mechanisms is the increase of activity of energy-dependent ABC membrane transporter proteins, called adenosine triphosphate (ATP) binding cassette output pumps, whose activity contributes to intracellular decrease in chemotherapeutic drugs [4]. Humans have 48 ABC genes, classified into seven subfamilies that differ in size architecture and domain arrangement. Among this group of proteins, the P-glycoprotein (P-gp/ABCB1) stands out, with protein 1 being associated with resistance to multiple drugs (MRP1/ABCC1) and breast cancer resistance protein (BCRP/ABCG2) [5]. Under normal conditions, efflux pumps are constitutively expressed in epithelial, excretory, and barrier tissues [6]. These proteins contain a transmembrane domain that binds and translocate substrates, which are connected to a pair of nucleotide-binding domains that bind and hydrolyze ATP to activate the import or export of substrates [7]. P-glycoprotein (P-gp), also known P-gp or multidrug resistance protein 1 (MDR1), is the most relevant transporter due to its participation in the absorption, distribution and elimination of a variety of drugs in various types of cancer [8].

Glycoprotein-170 (P-gp) characteristics

The multidrug resistance gene 1 (ABCB1) encodes P-gp, which acts as an energy-dependent pump to transport cytotoxic agents out of cells. Its expression is correlated with resistance to multiple drugs both in animal models and in numerous pathologies [9]. These drugs include colchicine, vincristine, vinblastine, taxol, actinomycin D, doxorubicin and adriamycin, in which resistance

to the selection agent is accompanied by cross-resistance to cytotoxic agents structurally and functionally not related [10]. P-gp is an ATP-binding cassette transporter (ABC), which uses the energy of ATP hydrolysis to pump substrates across the membrane, that has two transmembrane domains (TMD) and two cytoplasmic nucleotide binding domains (NBD). The TMD is composed of six hydrophobic transmembrane α-helices responsible for the recognition and transport of the substrate while the NBD participate in the generation of energy by the hydrolysis of ATP [11]. Many authors have suggested that P-gp has two states: the first is inward-facing and capable of binding intracellular transport substrates, and the second is outward-facing conformation that ejects substrates through the membrane (Figure 1) [12]. This protein contains a constitutive sequence of approximately 1280 amino acids, which are structured in two large hydrophobic domains with 43% homology, joined by linker [13]. In humans, there are 2 genes: ABCB1 and ABCB4 (the product of the ABCB4 gene is involved in the translocation of phosphatidylcholine in the plasma membrane), they are located on chromosome 7q21.1 and separated by 330 base pairs, in particular the ABCB1 gene comprises a 120 kb fragment and is made up of 28 exons and 28 introns [9-14]. P-gp is expressed in non-neoplastic tissue, this is shown in **Figure 2** [10,15].

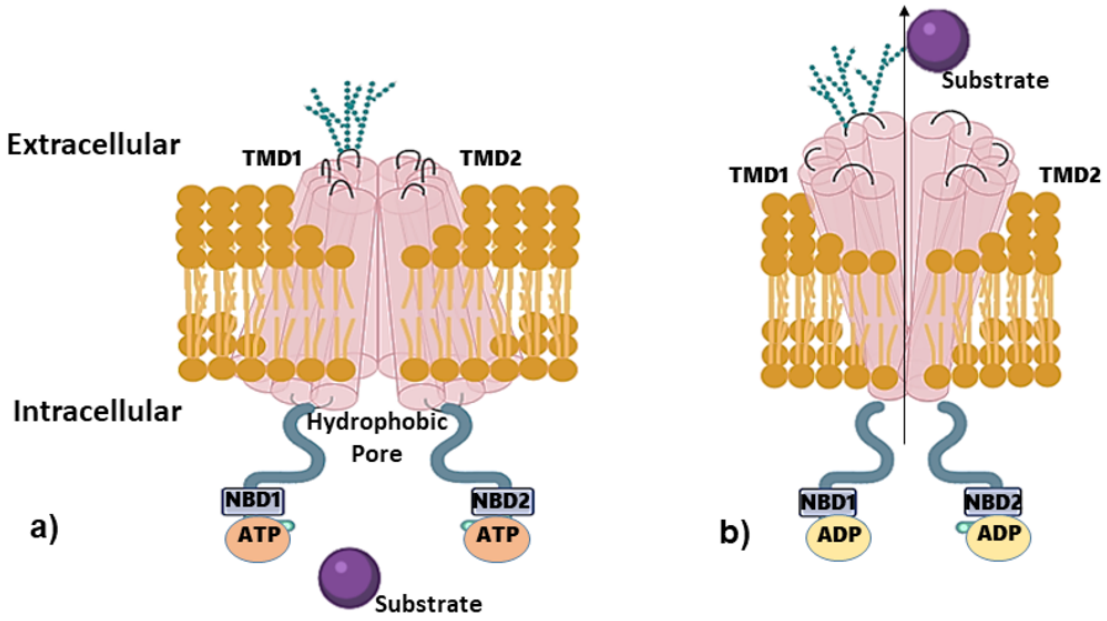

Figure 1: Gp-170 has been biochemically characterized as an integral plasma membrane glycoprotein that encompasses the lipid bilayer. It contains three pairs of alpha-helixes interspersed in the membrane, and a cytoplasmic domain that contains the ATP-binding site. It has three glycosylation sites in the region that emerges from the first extracellular loop of the protein and a structural conformation in twelve transmembrane domains that converge to form a pore or channel dependent on ATP hydrolysis. **a)** inward-facing conformation and **b)** outward facing conformation. Transmembrane domains (TMD) and nucleotide binding domains (NBD) [12].

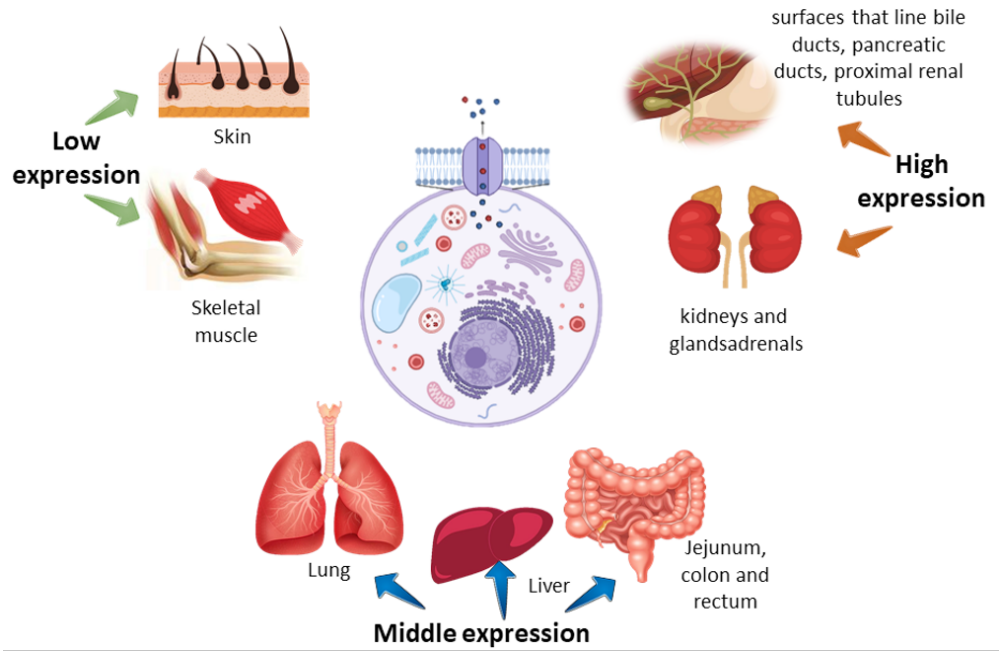

Figure 2: The expression levels of gp-170 are relatively high in non-neoplastic tissues indicating that the glycoprotein has a physiological role in secretory and protective processes, it is located on the luminal or apical surface of cells on the surfaces that line bile ducts, pancreatic ducts, proximal renal tubules, the jejunum, and the colon. Gp-170 has a cellular detoxifying function, it is also located in the physiological barrier in the cerebrospinal blood fluid, the blood-brain barrier and the blood-testis barrier [10]. It has been observed that the level of expression of mRNA has a differential expression, the highest levels are found in the kidneys and adrenal glands, intermediate levels in the lungs, liver, colon and rectum, and low levels in the skin. and skeletal muscle, as well as a very marked difference between the expression in pre-neoplastic and neoplastic tissues [10,15].

The substrates that the glycoprotein recognizes and expels do not have a biochemical or structural relationship, since there are hydrophobic, aromatic, non-aromatic, amphipathic molecules, cyclic, linear, basic, uncharged, zwitterionic, negatively charged, among others, with a molecular weight of 250 to 4,000, including lipids, phospholipids, xenobiotics, endogenous compounds, steroid hormones, cholesterol, and drugs that can also modulate glycoprotein activity, **Figure 3** [16-17]. Several molecules that are substrates of P-gp are of an amphipathic hydrophobic character, the way in which the molecules are expulsed is due to the fact that they can bind to the P-gp transporter in its inward conformation from the cytosolic side of the membrane. This glycoprotein is peculiarly flexible and supports the binding of molecules with high affinity and favors the binding of ATP in the NBD domain. These dimerize in a head-to-tail arrangement occluding the binding pocket of the intracellular environment, which leads to a conformational change that reorients the binding site to the extracellular side and results in the release of the substrate. The binding of ATP triggers the dimerization of NBD and the consequent hydrolysis of ATP which provides the energy for the change between these two conformations and redirects the TMDs to the outside of the cell membrane, which in turn open the pocket reducing the affinity of the substrates, resulting in the efflux of molecules to the outside **(Figure 1)**. The release of adenosine diphosphate (ADP) and inorganic phosphate (Pi) as products of this reaction reconverts P-gp to its initial conformation [17,18]. The flow dynamics of glycoprotein have recently been studied, Kopcho et al., showing that the high dynamics of the substrate-binding pocket in the TM domain demonstrates conformational flexibility that probably promotes substrate promiscuity, in addition to the occluded conformation that occurs in the pre-hydrolytic transport stage, the dynamics that make it undergo multiple correlated movements to promote the translocation of the substrate and thus prevent leaks reach the P-gp [12].

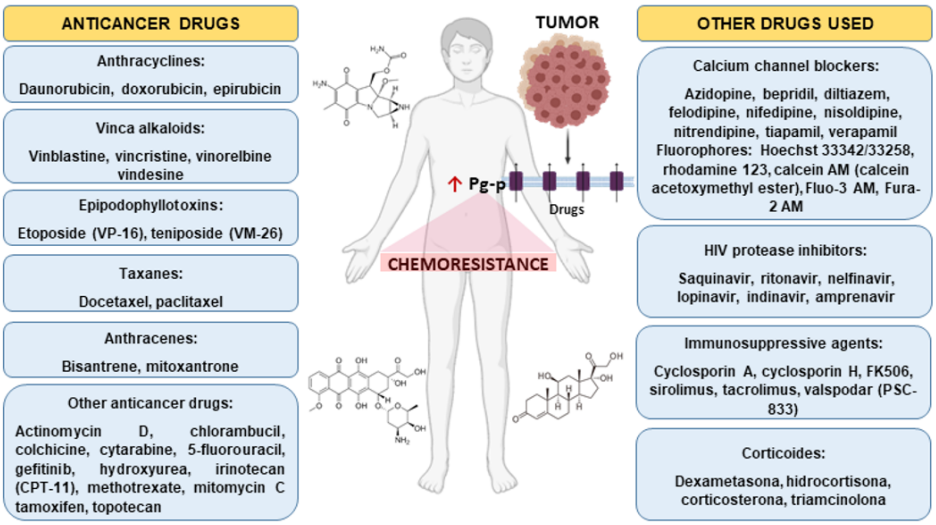

Figure 3. Within the chemotherapeutic schemes in cancer, various drugs used target the activity of gp-170, the molecules that are excluded by this glycoprotein are shown [16-17].

Regulation of P-gp expression by Hypoxia-inducible factor 1 (HIF-1)

Some cell signaling pathways play an important role in regulating the expression of the ABCB1 gene that encodes the expression of P-gp. It is known that chemotherapeutic agents activate pathways in response to the stress that is generated, which trigger the expression of genes in which ABCB1 is found and other genes that induce resistance [19]. Transcriptionally, P-gp is regulated by various transcription factors. The analysis of the promoter of the ABCB1 gene presents a sequence similar to a CAAT box located at -113 to -118 in relation to the transcription start site (+1) and a CCAAT box at -238 to -232. It requires an initiator element (Inr) at -3 to +5 for correct initiation and several consensus sites on the promoter for different transcription factors [19], that in different environments and under different stimuli modulate the expression of the glycoprotein.

Interestingly, it has been shown that the regulation of ABCB1 gene expression in tumor cells is related to the increase in focal areas that present prominent hypoxia, which are characterized by having a higher energy demand and a decrease in vascular areas. Comerford et al., reported that P-gp is increased in hypoxic conditions and consequently increase the outflow of digoxin and rhodamine. They performed quantitative microarray analysis of RNA and observed the increase of this glycoprotein in epithelial cells exposed to hypoxia in primary cultures and the analysis of multicellular spheroids showed greater resistance to doxorubicin. Although analysis of the promoter sequence of the ABCB1 gene identified a binding site for hypoxia-inducible factor 1 (HIF-1), and inhibition of HIF-1 expression resulted in significant inhibition of expression P-gp induced by hypoxia. The functional analysis of the ABCB1 promoter was carried out and it shows a significant increase in activity under hypoxic conditions, which shows that HIF-1 transcriptionally regulates the ABCB1 gene in response to hypoxia. These findings may show that hypoxia induces hypoxia expression of P-gp, which confers a mechanism of resistance to chemotherapy of some tumors [20]. On the other hand, the effects of hypoxia intensify the activity of other transcription factors that also participate in the regulation of the ABCB1 gene, as recently published by Antonio et al., where they show that HIF-1a transcriptionally regulates the factor of YY1 transcript, which in turn has been reported as a regulator of P-gp expression, this in a leukemic line, which could suggest that the effects of hypoxia would increase tumor susceptibility to drug resistance [21,22].

HIF-1 and its role in hypoxia

Hypoxia is a reduction in the normal level of oxygen tension in the tissues and is a very common characteristic of tumor development. The hypoxia happens due to the rapid proliferation of tumors outpaces the surrounding vasculature, as well of the aberrant new blood vessels formation that induces poor blood flow, which leads to the activation of multiple genes. Those genes are involved in different biological processes such as angiogenesis, glucose metabolism, survival, cell proliferation and, importantly, the development of resistance to the pharmacological action of various cytotoxic agents [23]. The key factor that regulates cellular adaptation to oxygen concentrations is hypoxia-inducible factor 1 (HIF-1), which is a heterodimer comprising α and β subunits, where the alpha subunit is highly sensitive to oxygen and it is stable only

under hypoxic conditions, in which it is translocated to the nucleus to dimerize with the beta subunit and is rapidly degraded under normoxic conditions, while the beta subunit or aryl hydrocarbon receptor nuclear translocator (ARNT) is expressed constitutively, both constitute the transcription factor HIF-1 [24-26].

In human, three isoforms have been reported of the alpha subunit of HIF, HIF-1α, HIF2α, and HIF-3α, of which HIF-1α is mostly overexpressed in tumor cells [27]. Post-translational modifications that regulate the stability and activity of the HIF alpha subunit depend mainly on the activity of prolyl-4-hydroxylases (PHD), in the presence of oxygen the HIF-1α subunits remain inactive through hydroxylation in proline residues of the HIF-α subunit, which triggers the activity of the von-Hippel-Lindau protein (pVHL) and the consequent degradation by proteasomes [28]. Under reduced oxygen conditions HIF-1α is stabilized, this is translocated to the nucleus from the cytoplasm where it binds to HIF-1 β, which leads to a conformational change and the formation of active HIF-1, this active heterodimeric complex binds to hypoxia response elements (HRE) of your target genes, **Figure 4 [29]**. HIF-1 activity can be affected by oxygen gradients through the regulation of HIF inhibitory factor, which, in the presence of oxygen, hydroxylates HIF-1α at asparagine residues at the C-terminal end, inhibiting the recruitment of coactivators, it has been reported that FIH-1 interacts with HIF-1a and VHL to mediate the repression of HIF1 transcriptional activity [30]. It should be noted that the percentages of oxygen tension in conditions in the tumor microenvironment is poorer than the oxygenation of its normal counterpart, but it has been described that it is considered hypoxia at concentrations ranging from 1% to 2% of O_2 or less than these values, although the tumor oxygen concentration depends on the initial oxygenation, the size and stage of the tumor as well as physiological conditions such as the network of blood vessels and the metabolic activity that it presents [31].

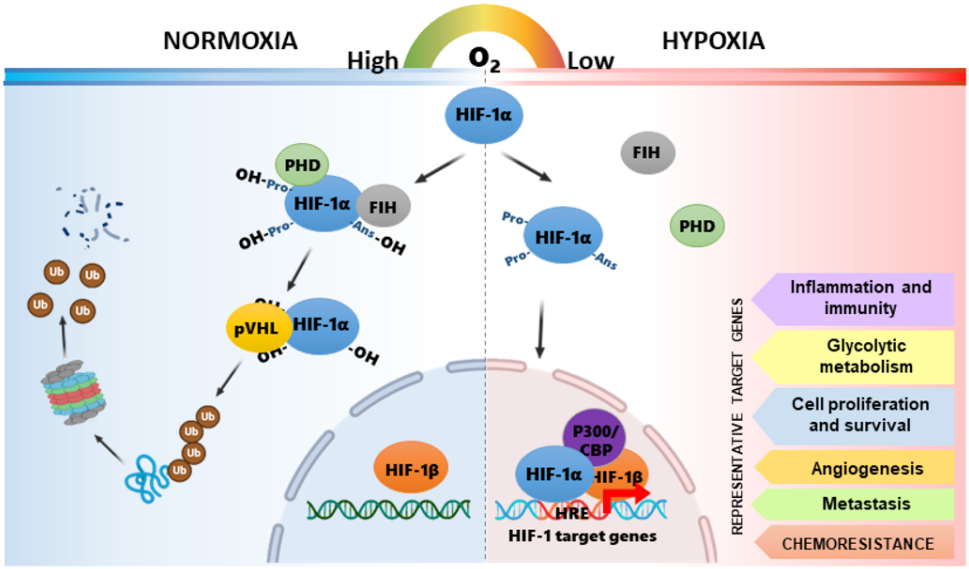

Figure 4. HIF-1 regulation. Normoxia, HIF-1α is hydroxylated by PHD, the hydroxylation is a target for pVHL for ubiquitination and proteasomal degradation. Factor inhibiting HIF-1 (FIH) hydroxylated an asparagine residue that blocks the binding of the coactivator p300 / CBP. In hypoxia, PDH and FIH are inhibited. HIF-1α is stabilized to dimerize with HIF-1β, and binds to target genes at the DNA, recruits p300/CBP, and activates transcription of several genes involved in inflammation and immunity, angiogenesis, metabolism, survival, proliferation, metastasis and chemoresistance [29].

The role of hypoxia in resistance to P-gp mediated chemotherapy in cancer

Hypoxia is an important factor that affects clinical outcomes by promoting genetic instability, tumor cell metastasis, invasiveness and chemoresistance. The irregular distribution of the tumor vasculature caused by persistent hypoxic conditions can result in an increase in the distance between the capillaries, exceeding the oxygen diffusion capacity. The tumor cells while adapting to this environment bring with them changes in gene expression that lead to changes in cellular and physiological functions that induce more aggressive and therapeutically resistant tumor phenotypes [32].

ROS in hypoxia and P-gp

Importantly, it has been described that the reduction in oxygen levels leads to the overproduction of reactive oxygen species (ROS), which includes oxyl radicals such as the superoxide anion [O2-], the hydroxy radical [HO×] and hydrogen peroxide [H_2O_2]. This happens because passage of electrons through the electron transport chain is reduced, which causes the alteration of the genetic material and the repair mechanisms [33,34]. Elevations in ROS concentrations can cause cellular damage to DNA and RNA, which promotes the mutation of molecules that induce the development of cancer and/or resistance to the pharmacological action of various molecules [34]. Elevated ROS levels have been reported to lead to tumor cell resistance through activation of redox-sensitive transcription factors such as NF-κB, Nrf2, c-Jun and HIF-1α [35]. It has been shown that ABCB1 mRNA and P-gp functionality is increased by raising intracellular ROS levels, in contrast, antioxidants (ascorbate, mannitol, dimethylsulfoxide, and N-acetylcysteine) markedly suppress the intrinsic overexpression of both the messenger and P-glycoprotein function, being highly sensitive to the effects of redox signals [36]. The levels of stability and expression of transcription factors can be regulated by ROS in hypoxic and non-hypoxic conditions. The most relevant is HIF-1α which is stabilized by oxidative stress induced by H_2O_2, while antioxidants markedly attenuate the accumulation of HIF-1α protein. It has been documented that ROS levels are elevated in hypoxia. This entails the stability of HIF-α, mediated by the inactivation of PHD through the oxidation of the ferrous ion that it requires for its catalytic mechanism [37]. Similarly, the effect that hypoxia has on the expression of HIF-1 and P-gp in relation to resistance to adriamycin in the human lung adenocarcinoma cell line A549 where both proteins are increased under hypoxia has been evaluated [38]. NOX1 plays a key role in the generation of ROS, its reduced expression increases the sensitivity to cisplatin in GBC-SD cells, while its overexpression inhibits it in SGC-996 cells because it increases the levels of intracellular ROS that activate the HIF-1α/P-gp pathway [39]. There are controversial data on the role of ROS in HIF transactivation and the consequent transcriptional regulation of ABCB1. An example of this is that when intracellular ROS are increased by glutathione depletion with butionine sulfoximine or glutamine starvation, which results in downregulation of Pgp during the growth of multicellular tumor spheroids, showing that these ROS are involved as second messengers in receptor tyrosine kinase signaling pathways and may act as negative regulators of Pgp expression [40]. While pretreatment with free radical scavengers such as vitamin E and vitamin C increased the expression of P-gp and HIF-1α in cells that overexpress Nox-1 [41]. The use of ROS generators such as emodin suppresses HIF-1 transactivation in response to hypoxia without changing HIF-1α expression and thereby reduces P-gp expression, promoting cisplatin retention [42].

The expression of HIF-1 and its correlation with P-gp in cancer cell lines

SSeveral investigations have shown that both ROS and acidosis induce differential expression of HIF-1α transcripts, and oxygen deprivation within the microenvironment of developing tumors can induce ABCB1 gene expression in a HIF-1 dependent manner, although there are reports that the activation of HIF-1 depends at least in part on the signaling through the activation of JNK, and this is independent of the generation of reactive oxygen intermediates [43]. In hypoxia, the nuclear HIF-1α / c-Jun interaction plays an important role in mediating the JNK-induced increase in binding of HIF-1 to HRE in the ABCB1 promoter, and requires the transcriptional coactivator p300 / CBP. JNK-induced down-regulation in hypoxia is mediated by increased binding of c-Jun to the AP1 site in the ABCB1 promoter, whereas JNK-induced up-regulation of ABCB1 in hypoxia is mediated by increased binding of HIF-1 to HRE in the ABCB1 promoter [25]. When it comes to reversing hypoxic environments, increased tissue oxygenation in vivo models, for example, through the use of a hemoglobin-based oxygen transporter, when combined with cisplatin treatment, clearly demonstrated that ABCB1 gene expression decreases significantly in the group in which the oxygen transporter PEG-Hb and cisplatin are applied. The decrease in the expression of HIF is observed in this group where the regions of higher expression of HIF-1α were far from the microvessels in cervical carcinoma xenograft [44]. The expression of HIF-1 and its correlation with P-gp and its effects on resistance to drug action has been evaluated using several cancer cell lines [45-57].

As far as cancer stem cells are concerned, much research suggests that they are sensitive to varying degrees of hypoxia and depend on factors such as HIF-1α and HIF-2α to maintain their stem cell characteristics, maintain quiescence, and contribute to the drug resistance through increased efflux pumps such as P-gp. Peculiarly, the PI3K / AKT pathway can activate both HIF1α and HIF2α and therefore ABC drug transporters, such as BCRP, MRP1 and P-gp, and lead to relapse events [58].

Recent studies performer for our group using a Bioinformatics analysis revealed three HIF-1α putative binding sites in the transcriptional factor Yin-Yang-1 (YY1) promoter region. Interestingly, we demonstrated that YY1 transcriptional regulates the expression of P-gp and its over-expression is correlated with poor prognosis in ALL pediatric patients [22]. In addition, we showed that high nuclear expression of YY1 correlates with poor survival in leukemia patients. Nevertheless, the role of these transcription factors in the pathogenesis of leukemia is not clear and given their possible co-expression and correlation with poor prognosis.

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Cell line	Findings	Ref
HepG2	↑ Hypoxic conditions → ↑ HIF-1α, ↑ gp-170, ↓ Apoptosis index decreases as the exposure time is extended.	[45] [46]
A2780	↑ Hypoxic conditions + shRNA HIF-1α → ↓HIF-1α, ↓ gp-170, ↑ sensitizing to apoptosis by paclitaxel	[47]
RKO, RKO-p53, T98G and H1299	Hypoxia with CoCl2+↑ HIPK2 →↑ HIPK2, ↓HIF-1α, ↓gp-170, ↑sensitizing to apoptosis by andriamycin.	[48]
MCF-7	shRNA HIF-1→↓HIF-1α, ↓gp-170↓resistance to paclitaxel; 3- (5'-Hydroxymethyl-2'-furyl) -1-benzylindazole or siRNA HIF-1α→ ↓gp-170, ↑ accumulation of intracellular doxorubicin in 3-D spheroids; ↑Hypoxic conditions → ↑AGR2 (joins with HIF-1α, stabilizers and delays its proteasomal degradation), ↑HIF-1α, ↑gp-170, ↑accumulation of doxorubicin.	[49] [50] [51]
PANC-1	↑ Hypoxic conditions + Epigallocatechin3-gallate→ ↓HIF-1α, ↓gp-170, ↓ apoptosis.	[52]
Patu8988 / 5-Fu	Hypoxia with CoCl2+ and the silencing at HIF-1α→ ↓HIF-1α, ↓gp-170, ↑ reverse the chemotherapy drug resistance.	[53]
RKO, LoVo and SW480	↑ Hypoxic conditions + ursolic acid → ↓ accumulation of HIF-1α, ↑ sensitivity to 5-fluorouracil and oxaliplatin. siRNA HIF-1α→ ↓gp-170 significantly, ↑sensitivity to the effects of adriamycin, vincristine, 5-fluorouracil and irinotecan.	[54] [55]
MOLT-4	Hypoxia with CoCl2+ co-cultured with mesenchymal stem cells→ ↑HIF-1α, ↑ gp-170, ↑ anti-apoptotic proteins.	[56]
RPMI8226 / L-PAM and ARH-77 / L-PAM	Melphalan+ echinomycin+ HIF-1α siRNA → ↓gp-170, ↑ drug sensitivity, ↑ cell death.	[57]

TABLE: 1

Expression of HIF-1 and its correlation with P-gp in human tumor samples

The importance of the correlation expression between P-gp and HIF-1 in human tumor samples has been demonstrated. The expression of both proteins was significantly higher in lymphatic invasion in colon carcinoma tissue samples classified as Dukes C or D stages, which involve lymph node metastases. Under hypoxic conditions inhibition of HIF-1α expression synergistically reduced P-gp expression in these cells. While in tissues from lung squamous cell carcinoma (LSCC) samples, the expression of HIF-1α and P-gp positively correlated and was associated with the poor clinical response and metastasis [59].

Sun et al. demonstrated that T24 and J82 bladder cancer cell lines became resistant to cisplatin when the expression of HIF-1α and P-gp is induced, which contributed to the proliferation, migration / invasion of these cells in tumor models in vivo, and are increased in samples of chemoresistant patients [60]. In hepatocellular carcinoma and normal adjacent tissue, the expression of P-gp is observed to be higher in liver tumor tissue compared to healthy adjacent tissue, while in the HepG2 cell line, when incubated in hypoxic environments [61]. The regulation of P-gp expression by miRNA in advanced by affecting hypoxia signaling gastric cancer was evaluated by Danza K et al. They showed that diminished expression of miR-20b, miR27a and miR-181a was associated with chemotherapeutic response in gastric cancer through increase HIF-1a and P-gp gene modulation, that was proposed as a possible novel strategy for the reversal of the

hypoxia effect on P-gp in this type of cancer [62]. Recently, Xu et al., show that the HIF-1 and P-gp relationship is controversial and seems in some situations does not exist because when evaluating the expressions of genes involved in multidrug resistant, including P-gp, MRP1, mTOR and HIF-1α. They demonstrated that the overexpression of the long non-coding RNAs-DANCR (l lncRNA-DANCR) markedly upregulated mRNA and protein levels of P-gp and MRP1 in both cancer gastric patients and cell lines, whereas expressions of mTOR and HIF-1α did not change. These results suggested that DANCR may contribute to the development of chemoresistance by regulating P-gp and MRP1 pathways [63]. In addition, it is demonstrated that the co-expression of P-gp and the tissue hypoxia markers HIF-1α, EPO and EPO-R in samples from patients with invasive breast cancer with lymph node metastases, a significant positive correlation was found between the positive tumors for HER2 that did not express steroid receptors and the expression of P-gp, in addition to a significant positive correlation between the expression of HIF-1α and P-gp in breast cancer [64].

There are many strategies that seek to identify markers based on the study of blood that correlate with the evolution of the disease. In a study to include adolescent and adult patients with acute myeloid leukemia, blood samples were analyzed to evaluate the correlation of HIF-1α expression with P-gp, only high expression of HIF-1 was found with unfavorable clinical evolution [65]. In addition, Rehman, et al. recently studied the expression of genes for resistance to chemotherapy associated with hypoxia in peripheral blood lymphocytes from patients with solid tumors and their correlation with the progression of the disease in peripheral blood from samples of patients with breast, ovarian, colon and prostate cancer. Although the results are not statistically significant differences, they found that there was an increase in the expression of 12-13 times of HIF-1α and 2 times greater in P-gp. They also found an association of the expression of HIF-1α, P-gp and LAPTM4B (which is a protein involved in resistance to chemotherapy by stabilizing HIF-1α) with advanced stages of the tumor, metastasis and chemotherapy [66].

In conclusion, the development of resistance has become a serious challenge for cancer therapies. Tumor cells acquire resistance through a variety of mechanisms and signals. Rapid cell proliferation can stimulate disorganized growth of new vasculature that limits oxygen distribution and induces cellular adaptation and leads to more aggressive and therapeutically resistant tumor phenotypes. The distribution of the vasculature not only limits the distribution of drugs within the tumor, but it also induces the expression of drug-eluting proteins such as P-gp, which are of great importance in addressing the clinical problem represented by tumor resistance to chemotherapy and which could be considered as prognostic and therapeutic targets.

In solid tumors, the hypoxic microenvironment determines a continuous ER stress, those two unfavorable conditions eliminate the most sensitive cells, but it trains the most resistant cells to survive and mount a network of adaptive responses to environmental stresses. This ability is plastic and determines the progressive acquisition of multiple resistances, including chemotherapy. As a result of this selective pressure, the most chemo-resistant and aggressive clones emerge during tumor progression. Since hypoxia induces pro-survival HIF-dependent pathways and chemoresistance, and an altered HIF-1 expression mediates chemo-resistance both in normoxia and hypoxia, disrupting these vicious circles may help in finding new chemo-sensitizing strategies or drug combinations

The pharmacological and mechanistic studies on the cross-talk between hypoxia, P-gp and chemoresistance, are useful to put together the pieces of the enigma linking these three players. Increasing our understanding on these pathways will direct pharmacological research towards more precise and effective approaches to counteract hypoxic and chemoresistant tumors in the next future.

Conflicts of Interest: The authors declare no conflict of interest.

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