The Role of Hypoxia and Exploitation of the Hypoxic Environment in Hematological Malignancies

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ABSTRACT

Tumor hypoxia is a well described phenomenon during the progression of solid tumors affecting cell signaling pathways and cell metabolism; however, its role in hematologic malignancies has not been given the same attention in the literature. Therefore, this review focuses on the comparative differences between solid and hematologic malignancies with emphasis on the role of hypoxia during tumorigenesis and progression. In addition, contributions of the bone marrow and angiogenic environment are also discussed. Insight is provided as to the role of hypoxia in metastatic spread, stemness, and drug resistance in hematologic conditions. Finally, emerging therapeutic strategies such as small-molecule pro-drugs and hypoxia-inducible factor (HIF) targeting approaches are outlined to combat hypoxic cells and/or adaptive mechanisms in the treatment of hematological malignancies.
INTRODUCTION

Hypoxia is a level of oxygen tension below the physiological level; physiological range varies due to diversified blood vessel network in different organs [1]. Hypoxic conditions develop during cancer progression due to rapidly proliferating tumor cells which reduces O₂ diffusion as well as impaired perfusion of the abnormal blood vessels in the tumor. The oxygen level in hypoxic tumor tissues is found to be less than 1.3% O₂, far below the physiologic oxygenation level (5-10% O₂) [2].

Cellular adaptation to hypoxia is mediated through protein stabilization of hypoxia inducible factor (HIF) subunits (HIF-1α, HIF-2α and HIF-3α) which are regulated by prolyl hydroxylase domain (PHD) and factor-inhibiting HIF-1 (FIH-1) enzymes. In oxygenated cells, HIF-α subunits are hydroxylated by PHD and FIH-1, poly-ubiquitinated and degraded by the proteasome; in hypoxia, the PHD enzymes lose their activity and the HIF degradation is halted. The stabilized, non-hydroxylated HIF-α translocate to the nucleus, where they dimerize with constitutively expressed HIF-β subunit, and binds to DNA to initiate gene transcription of the adaptive pathways [3, 4]. Cellular adaptations to hypoxia can also occur by HIF-independent mechanisms including mammalian target of rapamycin (mTOR) kinase, unfolded protein response (UPR) in response to endoplasmacytic reticulum stress [5], p38 MAPK, cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS) [6], NF-κB [7], and alarmins [8].

Hypoxia in solid tumors is widely involved in solid tumor biology including angiogenesis, metastasis and tumor resistance: The overexpression of HIF-α subunits in solid tumor is associated with aggressive cancer cell behavior and is correlated with poor overall survival of
patients [9]. In this review, we focused on recent insights into the hypoxic aspect of tumorigenesis and therapy in hematological malignancies.
THE ROLE OF HYPOXIA IN HEMATOLOGIC MALIGNANCIES

Physiologically, the BM shows the average oxygen tension between 5 - 7% O₂ [10, 11]. Due to the BM tissue architecture, there is a heterogenous O₂ level implied by the fact that the BM consists of at least two different niches, the osteoblastic niche the most hypoxic region of the BM and closer to the bone, and the well-oxygenated vascular niche closer to the blood vessels [12]. High levels of HIF-1α, was demonstrated at the border endosteal niche, whereas lower levels of HIF-1α were shown in the vascular niche [13]. Interestingly, the hematopoietic stem cells (HSCs) are localized mainly in the BM with the endosteal niche suggesting fundamental role of hypoxia in stem-cell function maintenance [14], such as homeostasis, low mitochondrial activity and increased glycolysis [15].

Development of hypoxia due to tumor progression

The development of hypoxic conditions during to progression of solid tumors was very well documented [16-19], and was shown to be mediated through a complex network of signaling pathways HIF dependent and independent pathways [3, 5]. Severe hypoxic conditions (beyond the physiologic BM conditions) were shown to develop during the progression of hematologic malignancies including multiple myeloma, lymphoma and leukemia.

Similar to solid tumors, BM samples from MM patients were reported hypoxic by using endogenous hypoxic markers, HIF-1α and HIF-2α [11, 20-23]. In animal models, the expression of exogenous pimonidazole (PIM) and endogenous (HIF-1α) hypoxia markers were significantly increased in the BM of mice with high involvement of myeloma compared to the BM of naive
mice or in areas with low tumor involvement [9, 18, 24]. In addition, a direct correlation was found between the tumor burden and the levels of hypoxia in the BM of mice with MM [18]. In addition to the BM, circulating MM cells were shown to have hypoxic phenotype [18]. In MM cell lines including KMM1, U266, RPMI8226, JJN3, U266, H929 and MM1s, HIF-1α was constitutively expressed and was further increased when the cells were exposed to hypoxia [9, 18, 21, 23]. In addition to hypoxia in the MM cells, the MM BM microenvironment also showed hypoxic response, in which strong HIF-1 and HIF-2 expression was detected in CD68+ macrophages [20, 22] and in stromal cells in areas with MM progression [18].

HIF-1 and HIF-2 were detected in 54% of Hodgkin lymphoma patients, and in 71% of non-Hodgkin lymphoma patients; and the expression of HIF-α, HIF-2α was found to play a role in tumor progression [25]. In diffuse large B-cell lymphoma (DLBCL), follicular lymphoma and mantle cell lymphoma (MCL), HIF-1α and HIF-2α proteins were highly expressed in 70, 73 and 73.5% of the patients; respectively [26, 27].

High expression of HIF-1α was detected in 67% of AML patients [28], 66.7% of pediatric ALL patients [29] with hypoxic areas widely present in ALL leukemic BM [30], and in 100% (10/10) of patients with B-cell CLL [31]. It was demonstrated that during leukaemogenesis in rat xenograft model of AML the BM became more hypoxic, detected by nitroimidazol, in which hypoxia was found in 80% of AML cells in the BM and 40% of circulating cells. [32]. Other reports showed that hypoxic regions expanded in the BM also in the mice xenograft models of ALL, AML and CML [30, 33, 34]. In CML model, hypoxia was shown to develop on the BM in correlation with the tumor burden, while no hypoxia was found in circulating CML cells [34].
Hypoxia was shown to develop during the progression of most types of solid tumors; however, the development of hypoxia in hematologic malignancies was variable. In myeloma and lymphoma, which have a more solid-nature in the BM, hypoxia was shown to develop in the BM of the patients in correlation with the tumor progression the BM, while in myeloma, circulating tumor cells had hypoxic phenotype. Leukemia involves both the BM and circulation but the number of circulating cells is way much higher and the dependency of leukemia cells on the BM is less critical. Accordingly, hypoxia in the BM was developed in different types of leukemia but less evidence was found for hypoxic phenotype in the circulating leukemic cells. We suggest that hypoxia plays a major role in the development of all three types of hematologic malignancies; but to a lower extent in leukemia.

The role of hypoxia in angiogenesis

In solid tumors, tumor neovasculogenesis plays a crucial role in the growth, progression and metastasis of cancer [16]. New blood vessels provide oxygen and nutrients, entrance for the immune cells, and exit of tumor cells into the circulation. Uncontrolled cancer cell proliferation causes hypoxia, which induces proliferation and sprouting of endothelial cells from pre-existing vessels, supports vessel maturation [1], and contributes to the recruitment of endothelial progenitor cells from the bone marrow to tumor areas and induction of their differentiation into endothelial cells [35].

An increase in vascular density in the BM, regulated at least in part by the HIF pathway, was demonstrated in myeloma patients during the MGUS to MM progression [36]. A positive
correlation was demonstrated between hypoxic markers such as HIF-1α and HIF-2α expression, pro-angiogenic factors (VEGF) and its receptors, circulating chemokine SDF-1, and the level of BM angiogenesis in MM patients [20, 22]. Culturing CD138+ cells from MM patients and MM cell line in hypoxia increased CXCL2, VEGF, TGF-β, and IL-8 secretion, induced expression of HIF-1α or HIF-2α and augmented angiogenesis in vivo [11, 22]. Subcutaneous injection of CD138+ MM cells with overexpressed HIF-1α and HIF-2α into the nude mice induced a number of pro-angiogenic molecules, which resulted in MM-induced angiogenesis in vivo [22]. On the other hand, silencing HIF-1α in MM cells reduced new vessels formation both in vivo [23] and in vitro [11].

Angiogenesis was shown to be involved in the pathogenesis and progression of non-Hodgkin lymphomas; matched lymph node biopsies at diagnosis and recurrence of relapsed/refractory indolent non-Hodgkin lymphomas patients showed increased vascular network and HIF-1α protein expression in the second biopsy, providing direct evidence that hypoxia-induced angiogenesis is an essential process for disease progression [37]. In anaplastic large-cell lymphomas, secretion of VEGF and angiogenesis was shown to be mediated through hypoxia-induced downregulation of microRNA-16 [38].

In leukemia, it was demonstrated that hypoxia contributes to angiogenesis through increased exosomes production by K562 leukemia cell line. This study shown that exosomes derived from hypoxic leukemia cells increased tube formation when cultured with endothelial cells, partially via augmented exosomal miR-210 expression [39]. In addition, silencing of HIF-1α in leukemic bone marrow stromal cells (BMSCs) from AML and ALL decreased production of pro-angiogenic factor (such as VEGF), and decreased angiogenesis [40].
These results suggest that, similar to solid tumors, angiogenesis in hematologic malignancies is induced by tumor hypoxia and targeting one of the hypoxic pathways, namely HIF, shows promising results in controlling formation blood vessel. Hypoxia-induced angiogenesis in hematologic malignancies was shown to be mediated mainly through local secretion of angiogenic factors and sprouting of local vessels; unlike solid tumors there is no evidence that hypoxia affects cell-trafficking of endothelial progenitors in hematologic malignancies. The effect of tumor hypoxia on endothelial progenitors and their contribution to angiogenesis in hematologic malignancies is yet to be explored. We suggest the inhibition of hypoxic response can provide an alternative approach to inhibit angiogenesis in which it will cause downregulation of multiple angiogenic factors at once, rather than inhibition of a specific factor.

The role of hypoxia in metastasis and spread

Hypoxia was shown to induce invasive behavior of epithelial cancer cells via epithelial-to-mesenchymal-transition (EMT) in which cells acquire plastic and migratory abilities [17, 18]. Tumor hypoxia was shown to activate EMT transcription factors [41, 42] and molecules responsible for polarization, adhesion, invasion of cells, such as vimentin, fibronectin, CXCR4, E-cadherin, MMP-2 and MMP-9 [17, 18].

MM is present at multiple sites of the BM and the tumor cells spread throughout continuous trafficking in and out of the BM [18, 43-45]. Steps of cell dissemination include: (i) cell detachment and acquisition of EMT-like phenotype (ii) invasion, (iii) egress to the bloodstream,
(iv) circulation in the blood, (v) homing to the predetermined tissues, (vi) formation of a new tumor foci, and finally (vii) growth of micrometastasis (colonization) [46]. The selective choice is believed to be triggered by multiple factors such as chemoattractants (SDF-1 and its ligand, CXCR4), growth factors (IL-6, TGF-β, IGF-I, IGF-II, FGF, PDGF, VEGF) and calcium [46]. Although not of an epithelial origin, Azab et al showed that increasing BM tumor volume caused tumor hypoxia which induced MM cell dissemination via hypoxia-induced EMT-like phenotype (increased expression of Snail1, FOXC2 and TGF-β) [18]. It was observed that, with increasing hypoxia, MM cells seemed to be less adherent to BM microenvironment (through down regulation of E-cadherin and down regulation of secretion of SDF1 from the stroma), and consequently a higher number of circulating MM cells in the peripheral blood was observed in mouse xenograft model [18]. At the same time, hypoxic MM cells (in the BM and in the circulation) expressed high CXCR4 through increased expression of HIF1α and facilitated migration and homing of MM cells to new normoxic BM niches [18].

In lymphoma, HIF-1α and HIF-1-signaling were increased during liver metastasis of T-lymphoma cells in vivo, and HIF-1α knock-down significantly impaired Met expression and phosphorylation and inhibited scattered liver metastasis [47].

In Leukemia, Azab et al demonstrated that hypoxia regulated trafficking of CML cells [34]. Hypoxia decreased the expression of E-cadherin CML cells in the BM and in vitro, which resulted in decreased adhesion to BM stroma. In addition, hypoxia increased CXCR4 expression in vivo and in vitro and enhanced chemotaxis. These results suggest that hypoxia in the BM induced an EMT-like phenotype in CML cells [34]. It was also reported that in AML, hypoxia increased CXCR4 expression, thus augmented migration and survival of leukemic cells [48].
Moreover, silencing HIF-1α applied in BMSCs, resulted in VEGF and SDF-1 reduction, and as a consequence decrease leukemia cell migration and adhesion [40]. No changes were observed in the expression of CXCR4 and E-cadherin in circulating CMLs as a result of hypoxia in the BM [34]. These results show that MM metastatic spread is very similar to the metastatic spread of solid tumors, showing hypoxic phenotype for MM cells in the BM and in the circulation which facilitates metastatic spread through and EMT-like mechanism. Inhibition of the hypoxic response as a therapeutic strategy to prevent metastasis in MM is yet to be explored. Although the literature in lymphoma is relatively limited, it seems that hypoxia plays an important role in the spread of lymphoma; more research to explore this role and its therapeutic applications is warranted. In leukemia hypoxia seems to play a critical role of the progression of the disease in the BM and it displays EMT-like phenotype, but not when the cells are circulating (in CML). However, the role of hypoxia in other leukemia types is still not clear.

The role of hypoxia in stemness and drug resistance

Hypoxia confers treatment resistance in solid tumors by regulating processes such as (i) cell cycle arrest (quiescence), a state of reduced cell proliferation which protects the cells from external stress [49, 50] [51], (ii) inhibiting apoptosis and senescence of cells, (iii) controlling autophagy, ER-stress, and p53 and mitochondrial activity [50, 52]. Hypoxia induces de-differentiated and immature phenotype of cells, as shown in neuroblastoma and breast cancer cells [53], as well as maintaining stem cell-like phenotype in both hematopoietic stem cells and in brain stem cells [14, 54, 55]. This was confirmed by activation of stemness-related genes and pathways, such as Oct4, HIF, Notch [56, 57], Wnt and Hedgehog [58, 59]. Hypoxic MM cells were shown to undergo de-differentiation, which was demonstrated by
decreased expression of plasma cell-specific markers (including CD138 and CS1) and transcription factors (IRF4, PRDM1 and XBP1), increased expression of B-cell-specific CD markers (CD20) and transcription markers (BCL6 and PAX5), and increased stem cell-like transcriptional program including Oct-4, SOX2 and NANOG [60]. Drug resistance is one of the main features of stem-cell-like phenotype which are both associated with hypoxia in solid tumors. It was demonstrated that by inhibiting HIF-1α in MM cells using echinomycin or siRNA against HIF, myeloma cells were sensitized to melphalan, which happened through reduction of one of the most important anti-apoptotic proteins, survivin [21].

Inhibition of HIF using echinomycin in mouse lymphoma stem cell population (characterized as c-Kit+Sca-1+) significantly reduced the colony formation of the lymphoma stem cells, indicating clear involvement of hypoxia in lymphoma tumor initiation [61]. Interestingly, VHL (protein involved in HIF degradation) transcript was undetectable in c-Kit+Sca-1+ lymphoma cells, which suggests the importance of HIF in maintaining stem-cell-like phenotype in lymphoma [61]. In addition, HIF-α protein stabilization was correlated with high expression of anti-apoptotic protein, Bcl-(xL), indicating that HIF-α is involved in apoptosis-resistance of lymphoma cells conferring drug resistance in non-Hodgkin lymphoma. [62].

In leukemia, using a mouse model of CML, it was demonstrated that HIF-1α is a key player in maintaining the survival of leukemia stem cells which present the phenotype of Lin−Sca-1−c-Kit+. HIF-1α deletion hindered propagation of CML by inhibiting cell cycle progression and inducing apoptosis. Interestingly, when compared to normal HSCs, leukemia stem cells seem to be more HIF-1α-dependent [63]. HIF-2α was also demonstrated to be strongly involved in the long-term repopulating ability of human CD34+ HSCs as well as in survival and engraftment ability of
primary human AML cells [64]. Inducible HIF-1α in AML cells changed the expression of 19 miRNA, among which miR-17 and miR-20a were downregulated by repressing c-Myc expression. These two miRNAs alleviated hypoxia and HIF-induced AML cell differentiation. Studies in vivo revealed that miR-20a contributes to HIF-1α-inducible differentiation of AML cells [65]. Overexpression of HIF-1α in hypoxic AML cell lines conferred chemoresistance to antimycin due to quiescence induced by cell cycle arrest [66]. Co-culture of ALL cells with stromal cells in hypoxia induced HIF-1α and induced AKT/mTOR signaling; inhibition of mTOR decreased HIF-1α and led to chemosensitization of ALL cells [33].

Altogether, unlike solid tumors were the contribution of hypoxia to the drug-resistant stem-cell-like phenotype is well established; these results suggest that hypoxia plays an important role in development of cancer stem cells and drug resistance in hematologic malignancies, but the data is still preliminary and needs further confirmation to provide direct evidence for the involvement of hypoxia in these processes. We suggest to further investigate the role of hypoxia in development of drug-resistant stem cell-like phenotype in hematologic malignancy this will have a huge impact on the our understanding of the development of resistance to therapy, development of minimal residual disease and recurrence in hematologic malignancies, and will open a new therapeutic window for enhanced treatments in the relapsed/refractor stages of these diseases. Special emphasis should be given to tumors involving stem cells and blasts.
Other effect induced by hypoxia

It was demonstrated that HIF-α plays an important role in bone biology and bone disease, since the bone is a physiologically hypoxic tissue [67]. Lytic lesions affect more than 80% of MM patients and are caused by imbalance between proliferation and activity of over-stimulated osteoclasts and suppressed osteoblasts. RANKL produced by MM cells and activating osteoclasts was shown to be increased in MM patients [68]. Recent reports suggest that osteoclast activity contributing to the osteolytic bone disease in MM is hypoxia-regulated, since the increase in number and size of osteoclasts was in part regulated by HIF-1α [23]. Stable inhibition of HIF-1α in MM cells halted pro-osteoclastogenic cytokines secretion including IL-7 and CCL3/MIP-1α, reduced the weight and tumor size in vivo, and significantly decreased bone destruction [23]. Osteolytic lesions were reduced together with tumor burden by HIF inhibition which can be explained by the fact that active osteoclasts support MM cell proliferation in vivo.
THERAPEUTIC STRATEGIES TARGETING TUMOR HYPOXIA IN HEMATOLOGIC MALIGNANCIES

Targeting hypoxia is an emerging strategy for the treatment of hematological malignancies, in which hypoxia-induced cellular adaptation mechanisms and hypoxic cells are being used as therapeutic targets for prevention of angiogenesis, metastasis, stemness and drug resistance.

Targeting hypoxia is an emerging approach to target tumor tissue and microenvironment, mainly due to the fact that hypoxia induces resistance to anticancer therapies. Some of the mechanisms of therapy-resistance include (I) increased expression of drug efflux pumps (such as P-glycoprotein, Pgp), (II) oxygen-dependent cytotoxicity of some drugs (such as bleomycin), (III) mutations conferring resistance, (IV) selection of cells insensitive to p53-mediated apoptosis, (V) decreased cell proliferation rate in hypoxic regions, and (VI) drug diffusion limits due to the distance from the blood vessels and thus inadequate exposure of cells to anticancer drugs (see Figure 1).

Targeting hypoxic cells with pro-drugs

Small molecule pro-drugs discovery in the 1970s was a result of an attempt to overcome the problem with hypoxia-induced radiation-resistance. It led to the finding of nitroimidazoles which can mimic the effect of oxygen and enhance the effect of radiation. Recently, a paradigm has shifted and hypoxia-activated pro-drugs are currently used as compounds that target hypoxia and HIF-mediated signaling pathways. This strategy is intended to penetrate the tissue and deliver cytotoxic agents to the hypoxic nutrient-starved regions of tumor areas with minimal toxicity for the surrounding normoxic cells [69]. In principle, non-toxic pro-drug
requires one- or two-electron reduction to a far more toxic radical, or further to a downstream product.

In solid tumors, some of the first pro-drugs such as metronidazole, misonidazole, etanidazole and tirapazamine have a very high toxicity [70]. Combination of these drugs with other chemotherapies enhanced the effectiveness of the treatment in vitro and in vivo [70] [71] [72] [73]. The combination of tirapazamine with cisplatin shows prolonged survival in phase III clinical trial; however, dosing is limited due to neutropenia and other toxicities [74]. No literature was found describing the use of these compounds in hematologic malignancies.

Two new pro-drugs, 2-nitroimidazole of the phosphoramide mustard, namely TH-302 and PR-104, also show potential in the clinical studies due to better dose potency compared to tirapazamine. TH-302 was shown to be cytotoxic against a number of human hypoxic cancer cell lines in vitro and in vivo [75-79]. TH-302 is being clinically tested in solid tumors as a therapy in combination with chemotherapy [69, 75], and has completed phase I clinical trial. TH-302 and PR-104 have been tested in myeloma and leukemia; anti-tumor activity of TH-302 was demonstrated both in vivo and in vitro in combination with bortezomib [24, 75]. Preclinical studies on myeloma model (5T33MMvv) showed that TH-302 induced MM cell apoptosis and decreased paraprotein secretion in vivo, and combination of TH-302 and bortezomib significantly improved survival of mice [24, 75]. TH-302 also effectively inhibited onset, progression of AML, and extended the overall survival, both in systemic AML xenograft models and mice with advanced AML disease. In vitro, TH-302 decreased HIF-1α protein expression and reduced ROS production, which resulted in decreased proliferation, increased cell cycle arrest and induced dsDNA breaks [80].
TH-302 is currently evaluated in phase I/II study in relapsed/refractory MM patients combination with dexamethasone, with or without bortezomib (NCT01522872). Dose limiting toxicity with most common adverse events such as leukopenia, thrombocytopenia, anemia and stomatitis were described. TH-302 in combination with dexamethasone scheduled twice weekly showed initial clinical activity with benefit rate in 33% patients who were relapsed refractory to both bortezomib and thalidomide/lenalidomide regimens. PR-104 is being evaluated in treating patients with refractory/relapsed AML in phase I/II study (NCT01037556), since leukemic BM was reported to be sufficiently hypoxic to activate PR-104 to its active metabolite PR-104H and PR-104M. The final report demonstrated that PR-104 had moderate toxicity (myelosuppression and enterocolitis) [81].

The hypoxic pro-drugs are showing promising results in preclinical and in clinical studies in hematologic malignancies as well as solid tumors; however their toxicity and pharmacokinetics appears to be a limiting factor in these treatments. We suggest further studies to development of a new generation of hypoxic pro-drugs with with greater hypoxic selectivity, less toxicity and well better pharmacokinetics; as well as more efficient vector for enhanced delivery of these drugs to hypoxic regions.

**Targeting HIF pathway**

HIF-targeted therapy is another promising approach to overcome hypoxia induced progression, metastasis and drug resistance. Although hypoxia does not equate HIF expression, since the HIF pathway is also regulated in normoxic conditions, HIF is strongly intertwined with almost every
aspect of cancer biology due to its powerful potential of regulating gene transcription. Recently, a high-throughput screening of FDA-approved drugs disclosed digoxin, acriflavine, anthracyclines (doxorubicin), vincristine, paclitaxel and many more as HIF inhibitors, which suggest that currently used drugs are already inhibiting HIF. However, based on their primary therapeutic functions, these inhibitors have also HIF-independent effects so their usage is not specific [82].

Silencing HIF-1α with shRNA successfully reduced MM-induced new vessel formation and tumor burden [11, 23]. In addition, inhibit HIF-α was proposed to target therapy-resistant stem cell-like phenotype in hematological CSCs [83]. Promising study in vivo demonstrated that HIF-1α inhibition using echinomycin in lymphoma [61] and leukemia [63] stem cells, efficiently decreased tumor-initiating activity of these cells and improved survival of mice. It was also showed that blocking HIF-α enhances the anti-proliferative effect of lenalidomide [23] and melphalan [21].

Further studies are warranted to investigate the therapeutic applications of inhibition of HIF in prevention of tumor progression, metastasis and drug resistance in hematologic malignancies. Furthermore, the development of more specific small molecule HIF inhibitors is urgently needed in the field to test these therapeutic applications.

**CONCLUSIONS**

Tumor-hypoxia was shown to develop in correlation with the progression of hematologic malignancies and is associated with aggressive tumor behavior. Exploiting the distinctive
features of hypoxia and hypoxia-regulated molecules in hematological malignancies is a promising strategy to improve the treatment of hematologic malignancies; however, its full potential is yet to be determined. We hypothesize that targeting hypoxia in hematologic malignancies, especially in MM and lymphoma, will improve the treatment in these diseases through inhibition of angiogenesis, metastasis and drug resistance.
REFERENCES


FIGURE LEGEND

Figure 1: Mechanism of hypoxic cells resistant to anticancer drugs

Hypoxia-associated mechanisms conferring therapy-resistance include (I) increased expression of drug efflux pumps (such as P-glycoprotein, Pgp), (II) oxygen-dependent cytotoxicity of drugs (such as bleomycin), (III) mutations providing apoptosis resistance, (IV) selection of cells insensitive to p53-mediated apoptosis, (V) decreased cell proliferation rate in hypoxic regions, and (VI) inadequate exposure of cells to anticancer drugs due to diffusion limit.
Increased drug-efflux mechanisms (Pgp)

Lack of O₂ required for cytotoxicity of drugs (bleomycin)

Increased mutation rates

Distance from blood vessels (diffusion limits)

Decreased cellular proliferation (quiescence)

Hypoxic cells insensitive to p53-mediated apoptosis
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