Chapter 18

The Critical Role of Hypoxia in Tumor-Mediated Immunosuppression

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Abstract

Underestimated for a long time, the involvement of the microenvironment has been proven essential for a better understanding of the cancer development. In keeping with this, the tumor is not considered anymore as a mass of malignant cells, but rather as an organ composed of various malignant and nonmalignant cell populations interacting with each other to create the tumor microenvironment. The tumor immune contexture plays a critical role in shaping the tumor immune response, and it is now well supported that such an immune response is impacted by the hypoxic stress within the tumor microenvironment. Tumor hypoxia is closely linked to tumor progression, metastasis, treatment failure, and escape from immune surveillance. Thus, hypoxia seems to be a key factor involved in creating an immune-suppressive tumor by multiple overlapping mechanisms, including the impairment of the function of cytotoxic immune cells, increasing the immunosuppressive properties of immunosuppressive cells, and activating resistance mechanism in the tumor cells. In this chapter, we review some recent findings describing how hypoxic stress in the tumor microenvironment hijacks the antitumor immune response.

Keywords: cancer, hypoxia, immune response, tumor microenvironment, autophagy, tumor plasticity, tumor heterogeneity

1. Introduction

Malignant cells are part of cellular and microenvironmental complexes which both define the initiation, progression, and maintenance of the malignant phenotype. In turn, malignant cells participate in creating a hostile microenvironment characterized by hypoxic areas within the

tumors. Indeed, the oxygen level in the hypoxic tumor is usually lower than that of corresponding normal tissue. The oxygenation level of tumor is likely depending on (i) the initial oxygenation of the tissue; (ii) the degree of the tumor heterogeneity; (iii) the tumor size and stage. **Table 1** summarizes the percentage of oxygen level reported as a median in some healthy organs and their corresponding tumors, as defined by several studies.

Healthy tissue/corresponding cancer	% of oxygen (Median)
Brain/brain tumor	4.6/1.7
Breast/breast cancer	8.5/1.5
Cervix/cervical cancer	9.5/1.2
Kidney cortex/renal cancer	7.0/1.3
Liver/liver cancer	4.0–7.3/0.8
Lung/nonsmall cell lung carcinoma	5.6/2.2
Pancreas/pancreatic tumor	7.5/0.3
Rectal mucosa/rectal carcinoma	3.9/1.8

Table 1. Comparison of the percentage (%) of oxygen level in different healthy tissues and in their corresponding cancers.

It is now widely appreciated that hypoxia is one of the most relevant factor involved in the impairment of the antitumor immune response by damping the cytotoxic function of immune cells. There are numerous studies supporting that hypoxic stress leads to the establishment of immune tolerance of tumor cells by preventing the migration and the homing of immune effector cells into established tumors. Furthermore, hypoxia can also drive tumor cell plasticity and functional heterogeneity and, thus, favors the emergence of more aggressive tumors. Many strategies are emerging for targeting intratumor hypoxia in order to change the immunosuppressive properties of the tumor to a microenvironment able to support antitumor immunity.

2. Hypoxia is the major factor of the tumor microenvironment

The long-lasting tumor immunology research has validated the concept of tumor immunosurveillance. The tumor immunosurveillance consists in the fact that cytotoxic immune cells recognize nascent transformed cells and destroy them before they become clinically apparent. Several types of immune cells are involved in the control of tumors such as immune effector and immune suppressor cells. Thus, cytotoxic T lymphocytes (CTL) belong to the adaptive immune system and they are able to recognize tumor antigens through the T-cell receptor (TCR) [1]. The antigens expressed exclusively by tumor cells are called tumor-specific antigens [2]. In addition to CTL, the tumor immune surveillance involves natural killer (NK) cells that belong to the innate immune system [1]. NK cells recognize tumor cells by mechanisms

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called "missing-self" and "induced-self" [3]. Briefly, NK cells are regulated by a balance of inhibitory and activating signals of surface receptors. Thus, NK cells can kill their target cell depending on the recognized ligand(s). The identification of activating or inhibitory ligands allows NK cells to distinguish between "self" versus "nonself" and "self" versus "altered self" by "missing-self" and "induced-self" recognitions. Indeed, the protection of normal cells from NK cell killing is achieved by balancing the stimulatory signals delivered by stimulatory ligands with inhibitory signals delivered by self MHC class I molecules. When the expression of self MHC class I molecules is lost following cell transformation or infection, the stimulatory signals delivered by the target cell remain unbalanced, leading to the activation of NK cells and lysis of target cells (known as missing-self recognition). Under some circumstances, transformed or infected cells overexpress stimulatory ligands that overcome the inhibitory signals leading to target cell lysis (known as induced-self recognition). It has been reported that both missing-self and induced-self recognition could operate simultaneously. In this case, NK cells display a high ability to discriminate between normal and transformed target cells [4].

In addition to cytotoxic immune cells, the tumor immune contexture contains immune suppressive cells such as myeloid-derived suppressor cells (MDSC) able to inhibit the function of immune effectors. Macrophages and neutrophil granulocytes are also involved in antitumor immunity [5]. These cells display tumor antigens and can stimulate other immune cells such as CTL, NK cells, or antigen-presenting cells (APC) [6]. Although both CTL and NK cells kill their target following the establishment of immunological synapse (IS) [7], the molecular mechanism by which they recognize their target tumor cells is fundamentally different. Two major pathways are used by CTL and NK cells to recognize and destroy tumor cells: (i) through the release by immune cells of cytotoxic granules containing perforin and granzymes and these cytotoxic granules are captured by tumor cells to induce cell death by apoptosis [8], and (ii) through tumor necrosis factor (TNF) superfamily-dependent mechanism [9].

It has been proposed that despite the powerful ability of the immune system to attack cancer cells, tumors can outmaneuver the immune effectors cells and escape the immune surveillance. It is now well documented that the ability of tumor cells to escape immune cell control is most likely resulted from the activation of several resistance mechanisms to evade effective and functional host immune response. Therefore, it stands to reason that established tumors, displaying multiple resistance mechanism, are likely not fully controlled by the immune system. In keeping with this, it is strongly believed that clinically detected cancers have most likely evaded effective antitumor immune responses. Recently, it has been reported that in addition to its role in protecting host against tumor development, the immune system can under certain circumstances sculpt the immunogenic phenotype of well-developed tumors. Such a mechanism favors the emergence of resistant tumor cell clones [10]. Accumulating experimental and clinical evidence suggest that the resistance mechanisms activated in tumor cells are multifactorial and that such resistance mechanisms are primarily evolved and activated in the tumor microenvironment [11]. It appears that hypoxia is the major tumor microenvironmental factor involved in the alteration of the transcriptome and the metabolome of tumor cells as well as their proliferation, survival, and invasion [12].

In this chapter, we summarize some recent findings describing how hypoxic stress in the tumor microenvironment regulates the antitumor immune response and leads to tumor escape from immunosurveillance. We focus on how hypoxia confers resistance to immune attack and impairs tumor cell killing mediated by CTL and NK cells.

2.1. Hypoxia and hypoxia-inducible factors (HIF) regulation

Tumor cells are able to adapt to hypoxic stress through the regulation of the hypoxia inducible factor family of transcription factors (HIFs) [13]. It has been reported for a large number of human cancers that HIFs were overexpressed and such overexpression is associated with poor response to treatment [14]. Moreover, evidence showed a clear positive correlation between enhanced hypoxic expression of HIFs and mortality [13]. Therefore, inhibition of HIFs could represent a novel approach to improve cancer therapies. Currently, efforts are being actively pursued to identify inhibitors of HIFs and to test their efficacy as anticancer therapeutics.

Three isoforms of HIF have been identified: HIF-1, HIF-2, and HIF-3. The hypoxia-inducible factor-1 (HIF-1) is the major factor mediating adaptive responses to changes in tissue oxygen level [15]. Indeed, HIF-1 is a heterodimer composed of a constitutively expressed HIF-1β subunit and an O_2-dependent regulated HIF-1α subunit. HIF-1α is a DNA-binding basic helix-loop helix of the PAS family [Per (period circadian protein); Arnt (aryl hydrocarbon receptor nuclear translocator protein); Sim (single-minded protein)] [16]. HIF-1α contains two oxygen-dependent degradation domains (ODDD), one in the N-terminal (N-ODDD) moiety and one in the C-terminal moiety (C-ODDD) [17, 18]. It also contains two transactivation domains (TADs), one N-terminal, which overlaps with the C-ODDD, and one C-terminal [19].

2.2. Regulation of HIF-1 level

The expression level of HIF-1α is determined by the rates of protein synthesis and protein degradation. While the synthesis of HIF-1α is regulated in an O_2-independent manner, its degradation is primarily regulated via an O_2-dependent mechanism. Thus, normoxic cells constantly synthesize HIF-1α protein and degrade it rapidly [17]. It has been shown that under normoxic conditions HIF-1α has a short half-life of less than 5 min [20]. However, under hypoxia or low oxygen level, the degradation of HIF-1α is blocked or dramatically decreased [21]. Under normoxia, HIF-1α is hydroxylated on proline residue 402 and/or 564 in the ODDD by prolyl hydroxylase domain protein 2 (PHD2) [17, 22]. Such oxygen-dependent hydroxylation of HIF-1α results in its binding to the von Hippel-Lindau tumor suppressor protein (pVHL). pVHL is the recognition component of an E3 ubiquitin-protein ligase complex that targets HIF-1α for proteolysis by the ubiquitin-proteasome pathway [23].

Enzymes regulating HIF-1α proteasomal degradation were first identified to be related to egl-9 in caenorhabditis elegans and to termed prolyl hydroxylase domain (PHD) enzymes (PHD1, PHD-2, and PHD3) [24, 25]. PHD2 uses oxygen as a substrate, and thus, its activity is inhibited under hypoxic conditions [25]. The inhibition of PHD2 leads to the inhibition of prolyl hydroxylation of HIF-1α and subsequently to the inhibition of HIF-1α-dependent proteasomal degradation. Consequently, HIF-1α rapidly accumulates in the cytoplasm, translocates to the

nucleus and dimerizes with HIF-1β. The HIF-1α/HIF-1β heteromeric dimer binds to the hypoxia responsive element (HRE) in target genes, recruits coactivators and activates transcription [14] (**Figure 1A**).

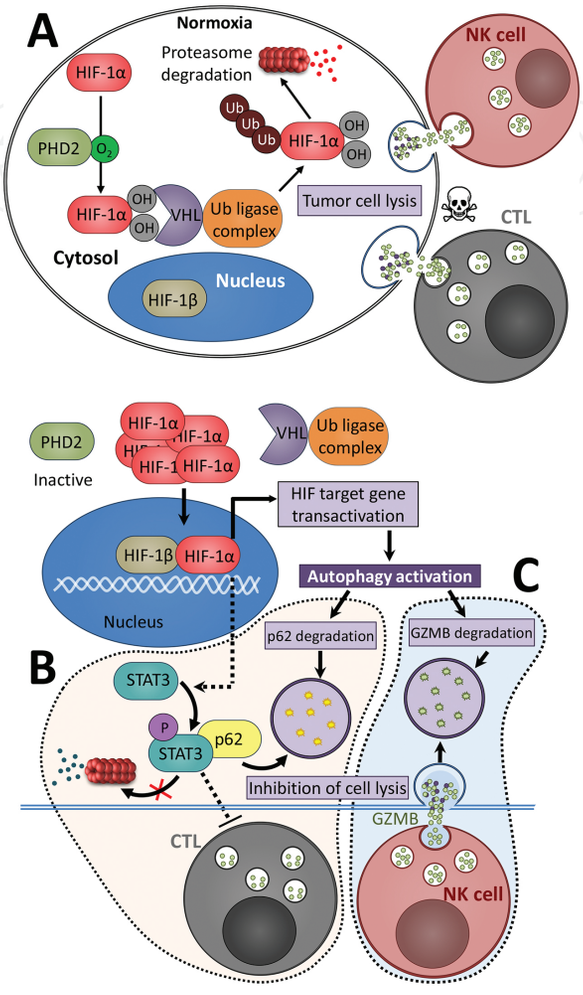

Figure 1. The role of hypoxic stress in the impairment CTL and NK-cell mediated lysis. (A) Under normoxia, the oxygen-sensitive prolyl hydroxylase domain protein 2 (PHD2) hydroxylates HIF-1α subunit. Hydroxylated HIF-1 interacted with Von Hippel-Lindau protein (VHL), subjected to ubiquitination and subsequently degraded by the ubiquitin-proteasome system. Under hypoxic stress, the function of PHD2 protein is blocked, HIF-1α is therefore stabilized and translocated to the nucleus to form heterodimeric complex with HIF-1β to transcriptionally induce the expression of HIF-target genes involved in several pathways such as autophagy. (B) Under hypoxia, STAT3 is phosphorylated at Ser-705 residue in a HIF-dependent manner by a mechanism which is not fully understood. (C) The hypoxia-dependent induction of autophagy leads to the degradation of the adaptor protein p62/SQSTM1, involved in targeting phospho-STAT3 to the ubiquitin proteasome system for degradation. Thus, targeting autophagy accumulated p62/SQSTM1 and therefore accelerated the degradation of phospho-STAT3. The degradation of phospho-STAT3 restores CTL-mediated lysis of tumor cells. In addition, the induction of autophagy in hypoxic tumor cells leads to the selective degradation of granzyme B (GZMB), a serine protease released by natural killer (NK) cells and contained in the cytotoxic granules. Such degradation inhibits NK-mediated lysis of tumor cells.

Using genomewide chromatin immunoprecipitation combined with DNA microarray (ChIP-chip) or DNA sequencing (ChIP-seq) analysis, it has been shown that more than 800 genes involved in several cell functions are direct targets of HIF [26, 27]. HIF-1 activates the

expression of these genes by binding to a 50 base pair cis-acting HRE located in their enhancer and promoter regions [28]. The HREs of all these genes contain the core sequence 5′-[A/G]CGT-3′, which in most cases is ACGTG [29]. It has been reported that HIF transcription factors preferentially bind to specific bases in the 5′ and 3′ proximity of the core that has led to define the following HRE consensus sequence [T/G/C][A/G]CGTG[CGA][GTC][GTC][CTG] [29].

Similar to HIF-1α, the stabilization of HIF-2α is also regulated by oxygen-dependent hydroxylation [30]. This could be related to the fact that HIF-1α and HIF-2α displayed a similar structure of their DNA binding and dimerization domains. However, the major difference between the structure of HIF-1α and HIF-2α is in their transactivation domains [31]. In terms of genes expression, both HIF-1α and HIF-2α share overlapping target genes, and each one also regulates a set of unique targets [32].

In sharp contrast with HIF-1α and HIF-2α, HIF-3α lacks the transactivation domain and could function as an inhibitor of HIF-1α and HIF-2α. It has been reported that the expression of HIF-3α is regulated by HIF-1 [33]. In addition to the regulation of the expression of a large number of genes, HIF family members regulate hypoxia-related microRNAs (HRM) [34] and some chromatin modifying enzymes [35].

3. Intra-tumor hypoxia: a key feature that triggers several resistance mechanisms of tumor evasion from immune surveillance

It has been clearly established that the immune effector activity and the antitumor immune response are significantly regulated by hypoxia. Indeed, hypoxia, via HIF-1α, decreases the susceptibility of lung cancer cells to CTL-mediated killing. It appears that the resistance to CTL is related to the effect of HIF-1α to induce the phosphorylation of signal transducer and activator of transcription 3 (STAT3) in tumor cells by a mechanism involving the vascular endothelial growth factor (VEGF) secretion. These data suggest that following its translocation to the nucleus, HIF-1α cooperates with pSTAT3 to impair lung carcinoma cell susceptibility to CTL-mediated killing [36] (**Figure 1B**). More recently, it has been shown that the expression of the phosphorylated form of STAT3 at Ser-705 residue is tightly controlled by the induction of autophagy in hypoxic tumor cells as the accumulation of pSTAT3 was no longer observed when autophagy was targeted genetically in tumor cells [37]. Autophagy is a catabolic cell degradation process. Autophagy plays an essential role in preventing accumulation of altered cell components [38] and as an adaptive metabolic response to provide nutrients. Recently, an unexpected role of autophagy in shaping the antitumor immune response [39] and the acquisition of resistance to TNFα has been shown [40]. Autophagy is activated under stress conditions such as hypoxia, nutrient starvation, growth factor withdrawal, and endoplasmic reticulum stress. It has been reported that the molecular mechanism by which autophagy regulates the pSTAT3 level involves the protein p62/SQSTM1 the ubiquitin proteasome system [37, 41].

Another study showed that in addition to the mechanism described earlier, it has been shown that the stem cell self-renewal transcription factor NANOG is also involved in the regulation of CTL-mediated tumor cell lysis [42, 43]. Hypoxia regulates NANOG at both transcriptional and translational levels and targeting NANOG in hypoxic cells restored CTL-mediated tumor cell killing. Furthermore, NANOG depletion results in the inhibition of STAT3 phosphorylation and its nuclear translocation. The hypoxia-induced microRNA (miR)-210 is also involved in the regulation of CTL-mediated tumor cells lysis. In fact, HIF-1 induces the expression of miR-210 which subsequently targets nonreceptor protein tyrosine phosphatase type 1 (PTPN1), homeobox A1 (HOXA1), and tumor protein p53-inducible protein 11 (TP53I11), and thereby decreases tumor cell susceptibility to CTL [44]. In the context of NK-mediated tumor cell lysis, it has been described that hypoxia increases the shedding of the major histocompatibility complex (MHC) class I polypeptide-related sequence A (MICA), a ligand for the activating receptor natural killer group 2 member D (NKG2D), on the surface of prostate cancer cells leading to an impairment of NO signaling [45] and subsequent escape of tumor cells from NK- and CTL-mediated killing. MICA expression is also downregulated by HIF-1 in osteosarcoma cells resulting in tumor resistance to NK-mediated lysis [46]. Through the activation of autophagy, it has been recently reported that melanoma and breast tumor cells escape NK-mediated lysis and that targeting autophagy in hypoxic tumor cells was sufficient to restore NK-mediated lysis. In this study, it has been shown that the activation of autophagy under hypoxia was responsible for the degradation of NK-derived granzyme B making hypoxic tumor cells less sensitive to NK-mediated killing [39, 47, 48] (**Figure 1C**). In line with the studies described earlier, it is now well admitted that hypoxic stress in the tumor microenvironment is a key factor involved in the control of antitumor immune response. Beside its role in impairing the function of cytotoxic immune cells, the immunosuppressive effect of hypoxia contributes to the emergence of resistant tumor cells that compromise the effectiveness of the anti-tumor immune response [49].

4. Hypoxia and tumor cell heterogeneity and plasticity

Solid tumors frequently reveal pronounced tumor cell heterogeneity with regards to cell organization, cell morphology, cell size, and nuclei morphology [50]. The molecular mechanisms underlying the phenotypic heterogeneity involve genetic, epigenetic, and environmental factors. It is now well established that hypoxia is an important contributor to intra- and intertumor cell heterogeneity [15, 51] by altering the expression of specific genes involved in cellular phenotype. In this respect, it has been reported that neuroblastoma cells and breast cancer cells lose their differentiated gene expression patterns and develop stem cell-like phenotypes under hypoxic stress [52, 53]. As a low stage of differentiation in neuroblastoma and breast cancer is associated with poor prognosis, it is strongly believed that, in addition to its contribution to tumor heterogeneity, hypoxia-dependent induction of tumor cell dedifferentiation contributes to tumor cell plasticity and aggressiveness.

Several lines of evidence suggest that tumor microenvironment drives stem cell renewal and differentiation. Indeed, poorly vascularized tumors contain hypoxic regions with undifferen-

tiated 'stem-like' tumor cells that survive under control of HIFs [54]. It has been reported that hypoxic stress in colon cancer inhibits the differentiation of tumor cells and maintains their stem-like phenotype [55]. In addition, myofibroblasts stromal cells secrete factors involved in maintaining cancer stem cells (CSC) population in colon cancer [56]. Furthermore, stromal cells drive a CSC phenotype on differentiated cancer cells, allowing a transient morphological heterogeneity observed in several cancers. In this regard, transient phenotypic changes from epithelial to mesenchymal (epithelial-mesenchymal transition (EMT)) or mesenchymal to epithelial (mesenchymal to epithelial transitions (MET)) phenotype, are initially considered as conversions facilitating cell plasticity but have recently gained appreciation as events involved in tumor heterogeneity [57]. In the context of tumor immunity, recent evidence revealed that tumor cell plasticity has serious implications in terms of immunological recognition and killing of the tumor, since such tumor cell plasticity may lead to the emergence of immunoresistant variants [58].

Although the role of the immune system in inhibiting early stages of tumor growth is well established, it is now strongly suggested that the immune system can also facilitate the advanced stages of tumor progression by sculpting the immunogenic phenotype of a developing tumor to favor the emergence of immune-resistant tumor cell variants. This has led to the concept of "immunoediting" which encompasses three phases: elimination, equilibrium, and escape. Thus, immunoediting allows tumors to evade immune destruction by becoming less immunogenic or more immunosuppressive [59]. Such adaptability, achieved through cell reprogramming, reflects an important property of tumors called immune-induced plasticity. While the molecular basis of immune-dependent induction of tumor cell plasticity and its effective contribution to the selection of tumor aggressive variants is still elusive, recent findings have revealed that activated CD8+ T cells can stimulate mammary epithelial tumor cells to undergo EMT and acquire the increased tumorigenic capability and therapy resistance of breast CSCs [60]. In this regard, it has been shown that reciprocal interactions between melanoma and immune cells enhances tumor cell plasticity and drives therapy resistance [61]. Based on these data, it is now well defined that targeting phenotypic plasticity should be considered for the development of novel therapeutic strategies with the ultimate goal to prevent the establishment of a more aggressive phenotype of cancer cells.

5. The clinical significance of targeting hypoxia

For many years, the major issue in the field of cancer immunity was to understand how cancer cells manage to evade immune surveillance despite the presence of a competent immune system. To address this issue, the major focus was on the mechanisms by which tumor cells escape cytotoxic immune cell recognition without considering the impact of the tumor microenvironment. This could partially explain why despite intense investigation, the gains provided by immunotherapy until recently are relatively modest. In addition, accumulating evidence suggests that tumor cell resistance mechanisms are likely evolved in the hypoxic tumor microenvironment. In keeping with this, it is therefore more accurate to consider cancer as a disease of the microenvironment rather than a disease of cells. Although remarkable

progresses have been achieved over the past two decades regarding the impact of the tumor microenvironment in cancer biology and treatment, its contribution in the development of tumor resistance to immune cell killing remains fragmented.

Emerging data indicates that hypoxia stress within the tumor microenvironment is a key factor involved in the impairment of the antitumor immune response. [62] Therefore, a deep understanding of the molecular mechanism by which hypoxia induces tumor resistance may contribute to the development of more effective tumor immunotherapies.

Consistent with the fact that hypoxia-dependent overexpression of HIF-1α is associated with an increased patient mortality in several cancer types, it stands to reason that inhibition of HIF-1 activity in preclinical studies would have marked effects on tumor growth and survival. In keeping with this, efforts are underway to identify selective inhibitors of HIF-1 and to assess their efficacy as anticancer therapeutics. Currently, two main approaches are used to target hypoxia in tumors, namely bioreductive prodrugs, and inhibitors of molecular targets upon which hypoxic cell survival depends [63, 64]. However, several lines of evidence indicate that the HIF pathway is technically extremely challenging to target. Indeed, the first evidence is that transcription factors in general, including HIF, have long been considered "undruggable," and therefore, no specific inhibitor of HIF has been brought to the market so far. The second evidence is that multiple levels of regulation and signaling pathways converge on and emerge from HIF [65]. Nevertheless, based on the molecular mechanism of HIF-1 protein, it has been suggested that small molecules could be used to inhibit HIF-1 activity through a variety of mechanisms including inhibition of (i) HIF-1α protein synthesis; (ii) HIF-1α protein stabilization; (iii) HIF-1α/β dimerization, and (iv) HIF-1/DNA binding. Two comprehensive recent reviews summarize these mechanisms in detail and give fairly exhaustive lists of the small-molecule inhibitors for each level [15, 66].

Using a cell-based assay, several small-molecule inhibitors of HIF-1 activity have been identified. Briefly, topoisomerase I inhibitors block the expression of HIF-1α via an undefined mechanism [67]. The small molecule YC-1 (3-(5′-hydroxy-methyl-2′-furyl)-1-benzylindazole) was also shown to reduce the level of HIF-1α by a mechanism that has not been established but at least is known to work independently from its function as a stimulator of soluble guanylate-cyclase activity [68]. YC-1 is not in clinical use. The HSP90 inhibitor 17-allyl-aminogeldanamycin (17-AAG) has been reported to induce the degradation of HIF-1α in a VHL-independent manner [69–71]. PX-12 (thioredoxin-1 redox inhibitor) and PX-478 are both inhibitors of HIF-1α protein expression and HIF-1-mediated transactivation [72, 73]. Finally, the disruptor of microtubule polymerization 2-methoxyoestradiol (2ME2) is able to decrease the expression of HIF-1α. Currently, only topoisomerase I inhibitors, camptothecin and topotecan, are clinically approved agents, PX-478, 2ME2, and 17-AAG are under evaluation in clinical trials, whereas YC-1 and thioredoxin-1 inhibitors are not in clinical use.

Despite of the anticancer effects of these agents could be related, in part, to their inhibition of HIF-1, it seems that none of these drugs specifically targets HIF-1. Although such lack of selectivity does not disqualify these drugs as anticancer agents, it enhances the difficulty to correlate molecular and clinical responses in patients. Therefore, the identification of more selective HIF-1 inhibitors in the near future is required and more investigation needs to be

done to identify novel potent and more specific inhibitors targeting clearly defined points in the HIF pathway.

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