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Review

Role of tumor hypoxia in acquisition of resistance to microtubule-stabilizing drugs

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ABSTRACT

Microtubules, an important cytoskeletal protein involved in mitotic and non-mitotic functions of cells, are important targets in cancer therapy. Microtubule-stabilizing drugs like the taxanes are critical adjuvant and palliative first-line therapies for the treatment of early, advanced and metastatic solid tumors of different lineages. Their adverse on- and off-target effects and high susceptibility to multidrug resistance, however, are major challenges encountered in the clinic in the treatment of solid cancers. Although biochemical resistance to microtubule-stabilizing drugs has been well characterized, molecular mechanisms that contribute to clinical resistance to taxanes in solid tumors still remain poorly understood and uncontrolled. The heterogeneous tumor microenvironment leads to greater diversity of resistance mechanisms to taxanes. Tumor hypoxia, a prominent feature of solid tumors, results in a broad range of effects on a number of cellular pathways and is one of the major contributors to the development of resistance to not only microtubule-stabilizing drugs but also other anticancer drugs. In this review, we highlight the potential role of hypoxia in the development of resistance to taxanes through mechanisms that involve altering the cell cycle, changing the properties of microtubules, and inducing the overexpression of gene products that contribute to drug resistance. Hypoxia-induced challenges described in this review are not limited to microtubule-stabilizing drugs alone, but in many cases also impact on treatment with non-microtubule-targeting anticancer drugs.

Contents

Abbreviations: 2-ME, 2-methoxyestradiol; CAIX, carbonic anhydrase IX; CSC, cancer stem cell; Dtx, docetaxel; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; FIH-1, factor inhibiting HIF-1; GSCs, glioma stem cells; HIF-1, hypoxia-inducible factor-1; HRE, hypoxia response element; MDR, multidrug resistance; miRNA, microRNA; MMAE, monomethyl auristatin E; MT, microtubule; MSA, microtubule-stabilizing drug; MTA, microtubule-targeting drug; mTOR, mammalian target of rapamycin; PHD, prolylhydroxylase domain; pHe, extracellular pH; pHi, intracellular pH; P-gp, P-glycoprotein; Ptx, paclitaxel; Sirt2, sirtuin 2; TUBB3, class βIII-tubulin; VEGF, vascular endothelial growth factor

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1. Introduction

Microtubules (MTs) are ubiquitous, hollow cylindrical cytoskeletal protein polymers that have diverse roles in eukaryotic cells. Due to their pivotal position in mitotic and non-mitotic functions of cells, they are one of the most important targets in cancer therapy. Classical MT-stabilizing agents (MSAs) like the taxanes are adjuvant and palliative therapies for the treatment of early, advanced and metastatic cancers of the breast, ovary, lung, and head and neck, as well as other solid tumors [1,2]. Although MSAs have proven to be useful in the clinic, their dose-limiting toxicities and high susceptibility to multidrug resistance (MDR) are major challenges to improve MSA-based chemotherapy.

The biochemical mechanisms that contribute to taxane resistance under normoxic conditions have been well characterized in cancer cells. These mechanisms include overexpression of drug efflux pumps, metabolism or conjugation of drugs, switching of expression to tubulin isotypes that are less susceptible, especially βIII-tubulin (TUBB3), altered interactions with MT-associated proteins such as tau, stathmin, MAP2, and MAP4, mutations in taxane binding sites, and changes to cytoskeletal structures [3–8]. In solid tumors, even greater diversity of resistance mechanisms exists, presumably stemming from the heterogeneous tumor microenvironment [9]. Accordingly, molecular mechanisms of clinical resistance to taxanes still remain poorly understood and uncontrolled [10].

The abnormal vasculature of solid tumors and the resulting limited supply of nutrition and oxygen create hypoxic regions that affect cancer progression and contribute to the resistance to chemotherapy and radiotherapy [11,12]. Tumor hypoxia has a broad effect on a number of cellular pathways and is one of the major contributors to the development of resistance to MT-targeting drugs (MTAs) and other anticancer drugs [13]. Herein, we review the potential role of hypoxia in the development of resistance to taxanes through mechanisms that involve altering the cell cycle, changing the properties of MTs, and inducing the overexpression of gene products that contribute to drug resistance. Hypoxia-induced challenges described in this review are not limited to taxanes alone, but in many cases also impact on treatment with non-MT targeting anticancer drugs.

2. Tumor hypoxia and hypoxia-inducing factor-1

Responses to hypoxia are mediated by hypoxia-inducible factor-1 (HIF-1), a protein heterodimer overexpressed in over 50% of solid tumors as a result of the hypoxic conditions inside the tumor (Table 1) [14,15]. Accordingly, HIF-1-positive patients in the clinic show significantly low 5-year survival rates compared to HIF-1-negative patients [14]. Necrotic regions of tumors show high levels of HIF-1α, indicating HIF-1α levels are regulated by tumor oxygenation (Fig. 1).

HIF-1 consists of two subunits, a constitutively expressed HIF-1β and an oxygen-sensitive HIF-1α. At low oxygen concentrations, HIF-1α dimerizes with HIF-1β, and the heterodimer acts as a hypoxic transcription factor, binding to the hypoxia response element (HRE) and activating or inhibiting multiple pathways that assist the cell to survive in a hypoxic environment [27,28] (Fig. 2). The coactivators, E1A binding protein p300 (P300) and CREB-binding protein (CBP), also interact with the HIF-1 heterodimer to activate transcription. Under normoxic conditions, HIF-1α is maintained at low levels by degradation in the proteasome, a process controlled by prolylhydroxylase domain (PHD) and factor inhibiting HIF-1 (FIH-1) proteins. PHD proteins act as oxygen sensors, hydroxylating the oxygen-dependent degradation domain of HIF-1α in normoxia and allowing VHL E3 ligase (von Hippel–Lindau E3 ligase tumor suppressor) to tag the protein for destruction [28]. A major theme of HIF-1α action is to reduce metabolism to protect cells under low oxygen conditions. Thus, HIF-1α translocates to the nucleus, forms a heterodimer with HIF-1β and inhibits ribosomal protein synthesis and mTOR (mammalian target of rapamycin) activation and its downstream effects, a protective response that also occurs in nutrient-limiting conditions [27]. AMP-activated protein kinase is stimulated by HIF-1 and plays an important role in altering metabolism during starvation to prevent the death of the cell. Targets of HIF-1, among many others, include glucose transporter genes, vascular endothelial growth factor (VEGF), platelet-derived growth factor, erythropoietin, and carbonic anhydrase IX (CAIX) [29–31].

In addition to the metabolic changes seen in response to HIF-1, the HIF-1 heterodimer also triggers the transcription of gene products that are associated with resistance to anticancer agents [32]. HIF-1α overexpression is associated with resistance to paclitaxel (Ptx), although another taxane, docetaxel (Dtx), downregulates the expression of HIF-1α in cancer cells [33]. Thus, Dtx, as an anti-HIF-1α agent and MSA, has been used to treat advanced hormone-refractory prostate tumors that show overexpression of HIF-1α [33]. Overexpression of HIF-1α in laryngeal cancer cells increases resistance to taxane-induced apoptosis through development of the MDR phenotype [34]. Downregulation of HIF-1α by siRNA improves accumulation and retention of doxorubicin, a non-MTA, DNA-damaging agent that, like taxanes, is also susceptible to MDR.

Altered expression of microRNA (miRNA) is known to play a significant role in the development of resistance to taxanes in the clinic [35,36]. Interestingly, a number of miRNAs are induced by HIF-1α in hypoxic conditions [37,38]. In addition to miRNA, tumor-infiltrating immune cells in the tumor microenvironment are also associated with resistance to anticancer agents in the clinic. Recent evidence suggests that hypoxia modulates the function and activity of immune cells, potentially implicating hypoxia-immune cell interactions in the development of resistance to anticancer drugs in solid tumors [39].

Expression of HIF-1α is not limited to hypoxic conditions since MAPK and PI3K pathway-mediated expression of HIF-1α has also been reported in normoxic conditions [40]. Transient overexpression of HIF-1α increases the invasive potential of melanoma that normally express low levels of endogenous HIF-1α. In contrast, siRNA downregulation of HIF-1α decreases anchorage-independent growth and Matrigel® invasion of highly metastatic melanoma cells that overexpress HIF-1α in normoxic conditions. The mechanisms by which HIF-1α signaling leads to acquisition of resistance to MSAs remain highly debatable; however, it is clear that HIF-1α-mediated activation of downstream pathways plays a significant role in development of MDR in the clinic [41].

Table 1
Expression of HIF-1α in various solid tumors.

Tumor type	HIF-1α level	References
Oropharyngeal	94%	[16]
Cervical	94%	[17]
Borderline ovarian	88%	[18]
Early-stage invasive cervical	81%	[19]
Oligodendroglioma	80%	[20]
Breast, lymph node-positive	76%	[21]
Ovarian	69%	[18]
Non-small cell lung cancer	62%	[22]
Breast	57%	[23]
Endometrial	49%	[24]
Head and neck	47%	[23]
Bladder	38%	[23]
Gastrointestinal stromal	32%	[25]

3. Altered MT dynamics and expression of class III β-tubulin in MSA-resistant hypoxic cells

There is evidence that hypoxia has significant effects on the changes in MT dynamics induced by an MSA. This effect may be due to conformational changes in tubulin that alter its susceptibility to MSAs. For example, hypoxia stabilizes MTs in tumor cells and increases their resistance to vincristine-induced disassembly via an early growth response 1

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