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Hypoxia in Tumor Microenvironment and Chemotherapy Resistance

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Abstract – Hypoxic region in tumors is characterized by an aberrant vascular network concomitant with cellular re-programming. This survival strategy in an aggressive tumor microenvironment, ultimately promotes tumor growth. Hypoxia-activated transcriptional factors such as HIF, NF-kB etc. govern tumor growth and progression. A large number of therapeutic methods have targeted this tumor's growth. However, development of resistance to treatments is one of the major problems. Hypoxia a component of tumor microenvironment plays crucial role in development of resistance to therapeutic approaches. In this review, we have summarized the most relevant findings to address the involvement of hypoxia in resistance to a variety of drugs. It is also discussed that hypoxia induced biological variations in tumor cells, which further facilitates chemo resistance. This will aid in grasping the key role played by hypoxia in chemo resistance and will be helpful in development of improved chemotherapeutic methods.

Keywords: Tumor; Tumor Microenvironment; Hypoxia; Chemo-Resistance

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HYPOXIA AS A TUMOR HALLMARK

Hypoxic microenvironment in solid tumors; concludes from an inequity between oxygen accessibility and consumption by rapidly multiplying tumor cells. The amount of available oxygen is further restricted by diffusion limitations (Carmeliet et al.2000; Hammond et al.2014). In 1908, it was the first time to report that hypoxic environment drives the up regulation of angiogenic factors to support the vascularization of growing tumor (Goldmann et al. 1908). Therefore the vascular network of tumor microenvironment is dissimilar from the vascular network of normal tissue. Different co-ordination of pro and anti-angiogenic factors lead to disorder architecture, vascular leakiness with non-laminar blood flow. Finally, this outcome of vascular network provides additional hypoxic region to the tumor microenvironment (Shah-Yukich et al.1988; Dewhirst et al.1989; Stenmark et al. 2006). In the tumor tissues, the measured partial pressure of oxygen is about 10-30mm Hg (1-3% oxygen) when compared to a partial pressure of 50-80mm Hg in the normal tissue (Vaupel et al. 2007). Another study of oxygen measurement was done in MCF-7 tumor xenografts, charted 1.8 mm Hg oxygen partial pressure in hypoxic core, as compared to 21.2 mm Hg partial pressure in normal tissue (Gogna et al. 2012).

Tumor hypoxia nurtures other hallmarks of tumor microenvironment and provides a favorable atmosphere for cancer progression (Gilkes et al. 2017). Hypoxia permits the selection of aggressive clones from a heterogenous tumor cell population, thus promoting the growth of a lethal phenotype (Vaupel, et al.2004, Rankin et al.2016).

Chemo therapy is one of the traditional modes of therapies, which is well recognized for cancer treatment. The hypoxic condition of tumor microenvironment is undoubtedly associated with the malignant progression and failed chemo-therapeutic approach. Therefore, hypoxic and non–hypoxic tumor cells with the comparable genetic framework differ in aggressiveness and resistance to chemotherapy. The aim of this review is to provide a combined information about the hypoxia induced resistance to a variety of chemo therapeutics.

HYPOXIC CELLULAR RE-PROGRAMMING IN TUMOR MICROENVIRONMENT

Hypoxic environment is known to induce variation in the behavior of cancer cells, which consists of changes at genetic, proteomic and metabolic levels, leading to subsequent extracellular matrix remodeling with increased migratory and metastatic behavior (Chi et al 2006; Casazza et al. 2014).

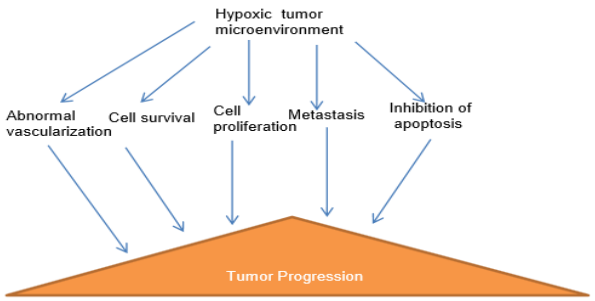

Figure1 Hypoxia is a hallmark of solid tumors, involved in multiple pathways to support tumor progression (Ruan et al. 2009).

Hypoxia induces extensive biological alterations that may contribute to the evolution of malignant tumor cells *i.e.* increased cellular proliferation (Harris *et al. 2002;* Hubbiet al. 2015),inhibition of apoptosis (Graeber et al. 1996), de-activation of DNA repair pathways (Yuan et al. 2000, Bindra et al. 2004, Koshiji et al. 2005*),* increased genomic instability (Coquelle et al. 1998*)*, up-regulation of growth factors and facilitation of tumor invasion and metastasis process (Rofstad et al. 2000; Subarsky et al. 2003; Monteiro et al.2017*).* Hypoxia induced adaptations in tumor cells allow them to overcome nutrient deficiency and promotes their survival in a truculent environment (Ackerman et al. 2014; Leithner et al. 2017; McNeil et al. 2017*).*

The three major hypoxia driven adaptations that have been studied in the tumor cells surviving in a hypoxic and low nutrient microenvironment are-

1. Angiogenic switch- A switch in equilibrium of pro-angiogenic versus antiangiogenic factors, favoring the former, leads to the construction of an abnormal vascular network (Liao et al. 2007).

2. Apoptotic deregulation- It includes alteration in the apoptotic pathways, allowing genetically unstable cancer cells to escape apoptotic destruction (Corn et al. 2005).

3. Glycolytic shift- It includes a metabolic shift in the cancer cells, from aerobic to anaerobic respiration (De et al.2008; Eales et al. 2016).

All above explained hypoxia induced variations in tumor cells enables resistance to chemotherapeutics by supporting the more lethal phenotype.

HYPOXIA FACILITATES CHEMO-RESISTANCE

The solid tumors are associated with a hypoxia-induced aberrant vasculature that leads to a micro environment with an inadequate amount of oxygen and nutrients. A diminished transport of chemotherapy drugs through this vascular network severely limits their efficacy (Vaupel et al. 2001, Vaupel et al. 2002, Trédan et al. 2007, & Aouali et al. 2017).

Hypoxia-induced resistance has been reported in number of anticancer drugs such as etoposide, 5-fluorouracil, docetaxel, cisplatin, gemcitabine, doxorubicin (Kalra et al. 1993; Yokoi et al. 2004; Song et al. 2006; Piret et al. 2006; Hussein et al. 2006; Wang et al. 2006; Hao et al. 2008; Ravizza et al. 2009; Hu et al. 2009). Other cytotoxic drugs, which lose efficacy in the hypoxic environment, are cyclophosphamide, carmustine, carboplatin, and melphalan etc. (Teicher BA et al. 1994; Littlewood et al. 2001; Cosse et al. 2008). Chemotherapy medications, consisting anthracyclines, mitoxantrone and Etoposide were used for evaluating the chemo-resistance of hypoxic MDA-MB231 breast cancer cells, where exposure of these drugs induces the high degree of heterogeneity in nuclear and cytoplasmic alterations in MDA-MB231 breast cancer cells (Sullivan et al.2008).

As copy number heterogeneity is a characteristic feature of tumors, which could be connected with the emergence of drug resistance in tumors, hypoxia has demonstrated to provide stimulus to generate temporary site-specific copy variations that could be an outcome in heterogeneity inside the tumors and cell populations (Black et al. 2015). Cisplatin a potent anticancer agent induces cancer cell death via DNA damage. However, hypoxia was found to involve in the reduced prognosis of this anticancer agent predominantly for patients with advanced stage of cancer (Cosse et al. 2008). Hypoxia works with autophagy to facilitate cisplatin resistance in lung cancer cells.

Cisplatin-induced apoptosis was studied in A549 &SPC-1 cells, revealing reduced cell death in hypoxia as compared to normoxia. However, on inhibition of autophagy, this reduction was significantly attenuated (Shamimi-Noori et al. 2008; Ulukaya et al. 2011; Wu et al. 2015). Hypoxia is also recognized to interrupt protein folding in the endoplasmic reticulum ultimately resulting in resistance to topoisomerase II-targeted drugs (Shen et al. 1987; Yun et al. 1995; Gray et al. 2005) and enhancing P-glycoprotein expression and multidrug resistance (Comerford et al. 2002). Hypoxia up-regulates the level of IL-1alpha, which shows a positive correlation with the tumor stage and resistance to Cisplatin in gastric cancer (Xuan Y et al. 2017). In other experimental studies, glioblastoma has shown to resistant against anti-angiogenesis treatment, where hypoxia plays a strategic role via enhanced invasion and migration, a shift in cellular metabolism, up-regulation of HIF

mediated downstream processes (Mahase et al. 2017).

Thus, hypoxia brings large events of biological variations in tumor cells to support their survival subsequently contributing to aggressive phenotype & therapy-resistance. In this context, hypoxia-inducible factor-1(HIF-1) is the most-studied transcription factor, accountable for adaptation of cells to hypoxia and effectively participates in chemo resistance and aggressiveness of tumors (Dai et al. 2003; Brown et al. 2006; Ravizza et al. 2009). HIF-1, first described by Wang and Semenza in 1995, has appeared as a central transcriptional controller of adaptive developments that facilitates tumor growth via proliferation, invasion, and metastasis (Semenza et al. 2000; Gordan JD et al. 2007; Shah T et al. 2015).

Explanation of the molecular source behind the drug resistance and HIF's participation in this is a complicated task as it varies according to tumor type; Rohwer et al. have summarized the literature to understand the HIF-mediated chemotherapy failure and its molecular basis.

Cancer Cell model	Drug/molecule	Molecular basis	Reference
Glioma cells	Etoposide, doxorubicin	MRP1	Chen et al. 2009
Glioblastoma cells, colon cancer cells	Adriamycin	P-gp	Nardinocchi et al. 2009
Gastric cancer cells	Multiple drugs	P-gp, MRP1	Liu et al. 2008
Breast cancer cells	Methotrexate	P-gp	Li et al. 2006
HCC cells	5-Fluorouracil	P-gp, MRP1, LRP	Zhu et al. 2005
HeLa cells	4-HPR	Beclin1	Liu et al. 2010
Gastric cancer cells	5-Fluorouracil	p53, NF-B	Rohwer et al. 2010
Prostate cancer cells	Flutamide	Bcl-xL	Chen et al. 2009
Glioblastoma cells, colon cancer cells	Adriamycin	Bcl-2	Nardinocchi et al. 2009
HCC cells	Etoposide	Bak	Sermeus et al. 2008
Fibrosarcoma cells	Cisplatin	Bid	Hao et al. 2008
Gastric cancer cells	Multiple drugs	Bcl-2, Bax	Liu et al. 2008
Breast cancer cells	Docetaxel	Survivin	Peng et al. 2006
Neuroblastoma cells	Etoposide,	Vincristine	Hussein et al. (2006)
Pancreatic cancer cells	5-Fluorouracil, doxorubicin,	Survivin	Chang et al. (2006)
Fibrosarcoma cells, colon cancer cells	Etoposide	Bid	Brown et al. (2006)
HNSCC cells	Paclitaxel	Bid	Ricker et al. (2004)
Colon cancer cells	Etoposide, oxaliplatin	Bid	Erler et al. (2004)
Gastric cancer cells	5-Fluorouracil		Rohwer et al. (2010)
Breast cancer cells, prostate cancer cells	Etoposide	Topoisomerase II alpha	Sullivan and Graham (2009)
Mouse embryonic fibroblasts	Etoposide		Wirthner et al. (2008

Figure 2 an overview of HIF-1 induced chemoresistance in a different type of cancer cells (Rohwer et al.2011).

Despite of this HIF-1 independent chemo-resistance in hypoxic tumors have been reported, (Dong et al. 2001; Kilic et al.2007) involving nutrient starvation, acidosis, enlarged interstitial fluid pressure and passage of less drug amount. Additionally, this hypoxia mediated& HIF-1 independent resistance of tumor cells is explained by a large number of reasons includes anti-apoptotic factors eg.IAP3and Bcl-2 family proteins expressed independent of HIF-1, activation of the PI3K pathway, nuclear factor kappa-B (NF-κB), cycloxygenase-2 (COX-2), activator protein-1 (AP-1), cjun, Pim-1, and STAT-3. However, the amount of their relation with the HIF-1 is uncertain (Dong et al. 2001; Yokoi et al. 2004; Piret et al. 2006; Chen et al. 2009;Selvendiran et al. 2009).

SUMMERY

Tumor hypoxia is a result of uninhibited tumor growth coupled with an inadequate blood supply through the aberrant vascular network. Adaptation of tumor cells to hypoxia is a result of well-coordinated expression of a wide spectrum of genes. Emerging evidences suggest that tumor hypoxia is a major concern in the tumor biology, due to its crucial role in tumor cell proliferation and therapeutics resistance. Hypoxia induced signaling events initiate the process of neo-angiogensis coupled with cellular reprogramming which lead to emergence of increasingly aggressive tumor cells that are resistant to chemo-therapeutic strategies. The purpose of current research is to target the hypoxic tumor micro-environment with improved chemo-therapeutic methods.

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